9.12.76
COK-H01375-4-P024263

September 1, 1976
volume 126, *number* 1

(4)

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

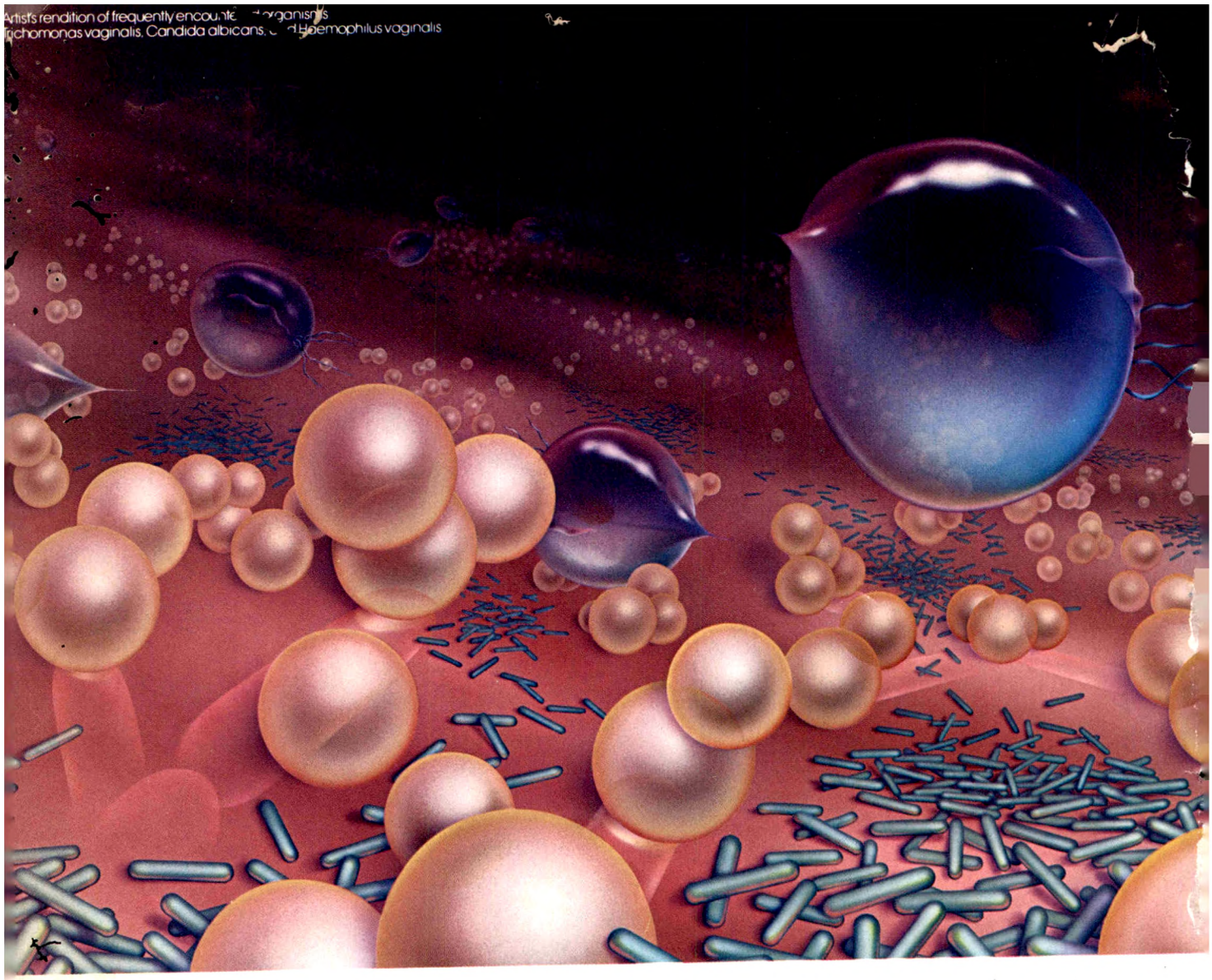
Official Publication

AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Published by

THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (1) 1-150 (1976)



VAGINITIS*

VAGITROL®

CREAM
(sulfanilamide 15.0%, allantoin 2.0%, aminiacrine hydrochloride 0.2%)

SUPPOSITORIES
(sulfanilamide 1.05 g, allantoin 0.14 g, aminacrine hydrochloride 0.014 g)

Usually uncomfortable and embarrassing, your patient wants fast relief.

Prompt symptomatic relief† of itching, burning, discharge, malodor.

Often more than one pathogen is involved.

. . . when the specific organism is unknown.

*This drug has been evaluated as probably effective for this indication. See brief summary.

See preceding page for summary of prescribing information.

NOTE:
If possible, base treatment on specific diagnoses from sound clinical and laboratory methods.

INDICATIONS

Based on review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

†"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually Trichomonas vaginalis, Candida albicans, or Haemophilus vaginalis) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to Haemophilus vaginalis or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS

Hypersensitivity to product ingredients or sulfonamides. Kidney disease.

WARNINGS

Pregnancy: Safe use not established. Teratogenic potential of sulfonamides not thoroughly investigated. However, a significant increase in the incidence of cleft palate and other body abnormalities of offspring was observed when sulfonamides were given to pregnant rats and mice at high oral doses. Usefulness of sulfonamides is limited due to increasing frequency of resistant organisms. Sulfonamide associated deaths were reported from hypersensitivity, agranulocytosis, aplastic anemia, other blood dyscrasias. Early clinical indications may be sore throat, fever, pallor, purpura, jaundice.

Discontinue on evidence of systemic toxicity.

PRECAUTIONS

Give with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Maintain adequate fluid intake to prevent crystalluria and stone formation. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. (Frequently dose related.)

ADVERSE REACTIONS

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme (Stevens-Johnson Syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis.

Gastrointestinal reactions: Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia.

Misc.: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosum and L.E. phenomenon. Sulfonamides bear chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely. Cross-sensitivity may exist with these agents.

Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides. Long-term administration has produced thyroid malignancies in the species.

SYNTEX
SYNTEX LABORATORIES, INC.
PALO ALTO, CALIFORNIA 94304



Fast, accurate information . . .

when you need it, wherever you need it, from Sonicaid's battery powered, portable, fetal heart detectors.
Sonicaid also manufactures a comprehensive line of AC powered fetal heart detectors and fetal/maternal monitors. Write or phone Executive Vice President John Scales today for complete information.

D205 Portable Diagnostic Fetal Heart Detector
directional, ultra-sound transducer's output fed to stethoscope-style headset, loudspeaker or tape recorder.



SONICAID
P.O. Box 714 Fredericksburg, VA 22401 (703) 898-6820 Telex 827304

(P 24,263

Comprehensive Group Health Care Plan
(Winston-Salem, North Carolina)

A new prepaid group health plan (Multi-specialty) opened July, 1976, for employees of R.J. Reynolds Industries, Inc. Assured growth, continuing expansion. The following board-qualified specialists are needed:

INTERNISTS PEDIATRICIANS OB/GYN

This represents an opportunity to practice under ideal conditions in modern new facilities and excellent hospitals. Medical school environment.

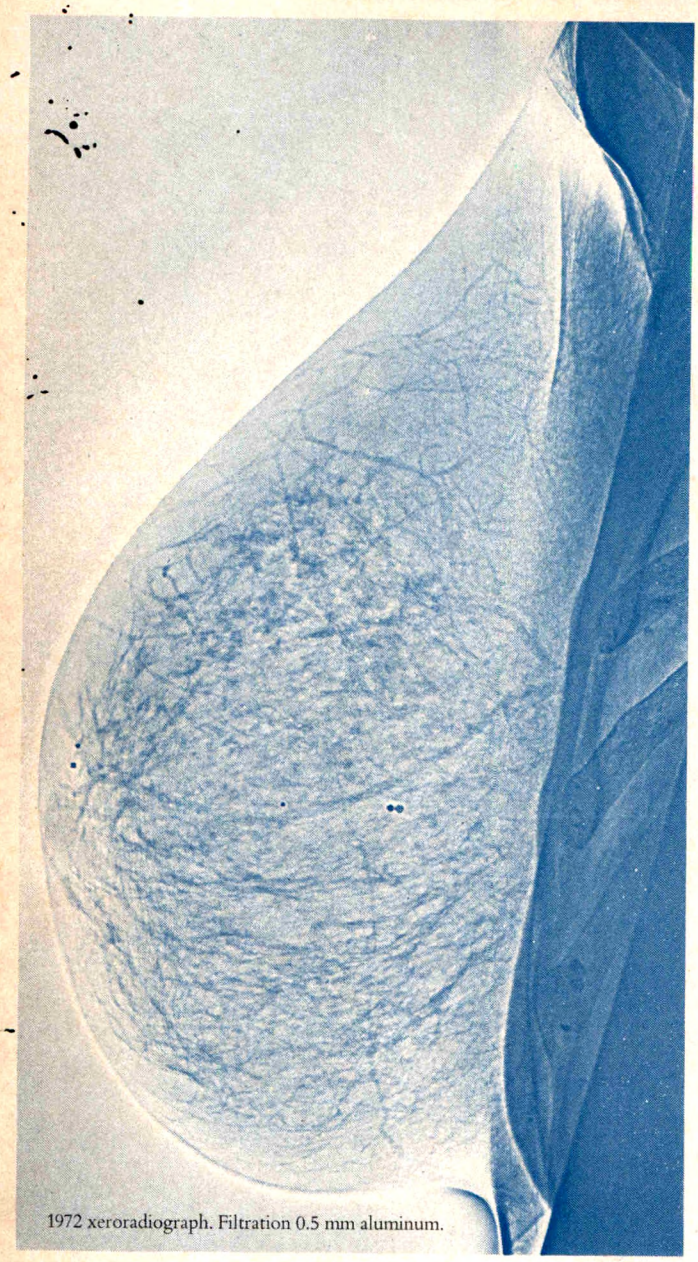
Winston-Salem is located in the Piedmont section of North Carolina and is within reasonable driving distances to the Atlantic Ocean and Blue Ridge Mountains. The city is noted for its cultural, recreational, and college environments.

Salary commensurate with experience, Liberal fringe benefits including paid vacation, CME, retirement, life insurance, and health coverage. Malpractice insurance paid. Relocation expenses paid.

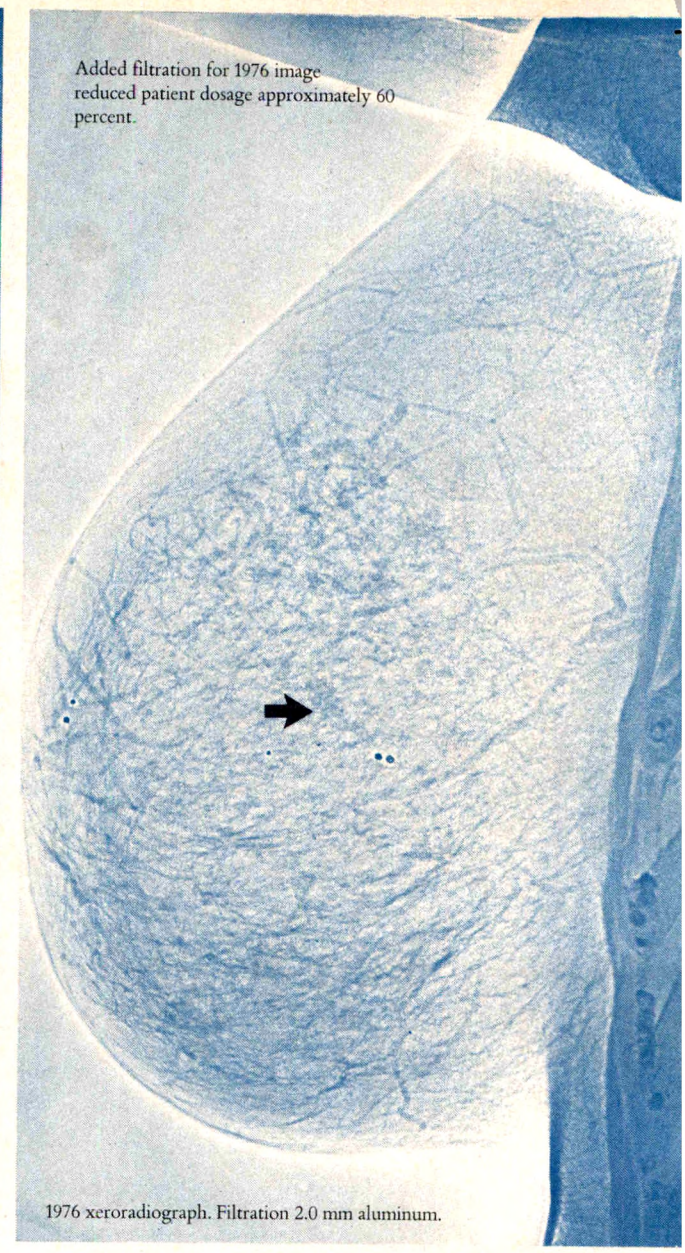
Send curriculum vitae, including salary requirements to:

Reid Bahnson, M.D.
Medical Director
W-S HEALTH CARE PLAN, INC.
250 Charlois Blvd.
Winston-Salem, North Carolina 27103

Winston-Salem Health Care Plan Inc.
An Equal Opportunity Employer M/F



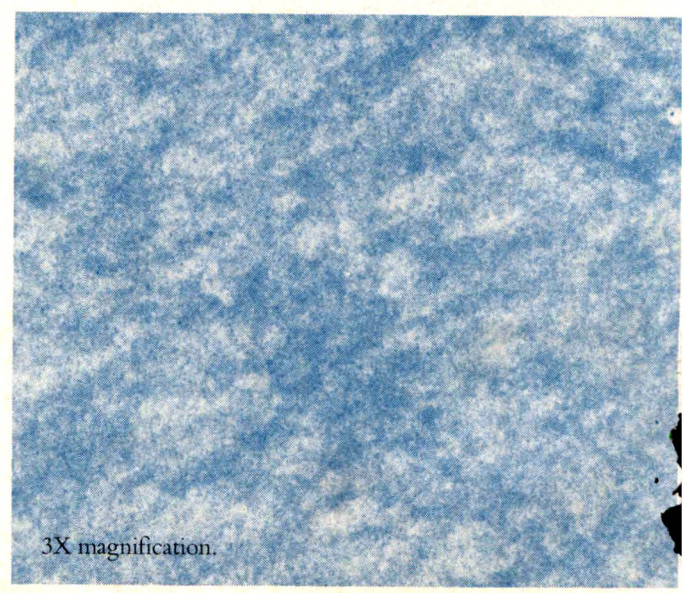
1972 xeroradiograph. Filtration 0.5 mm aluminum.



Added filtration for 1976 image reduced patient dosage approximately 60 percent.

1976 xeroradiograph. Filtration 2.0 mm aluminum.

Case history: 63-year-old patient, examined in 1972 because of pain in left breast (right breast previously removed.) Routine follow-up in 1976 revealed occult nonpalpable carcinoma (arrow.) Pathological findings: 3 mm ductal carcinoma with no axillary node involvement. (Images from Gloria Frankl, M.D., Dept. of Diagnostic Radiology, Kaiser Permanente Hospital, Los Angeles, CA 90027.)



3X magnification.

We're making it even safer for her.

Xeroradiography is the most widely used method for early detection of breast cancer. Its remarkable detail makes it easier for radiologists to identify very early nonpalpable or occult carcinomas.

The radiation dosages required for mammograms with xeroradiography have been low. However, the growing trend among physicians is to refer their high-risk patients for periodic mammography, and this has focused attention on long-term radiation exposure.

Now the results of a carefully controlled program of laboratory experiments, and clinical work by practicing radiologists, demonstrate that xeroradiography dosages can be dramatically reduced by using increased filtration.

Even when dosages are 60 percent lower than those previously required, the unique xeroradiographic quality is preserved.

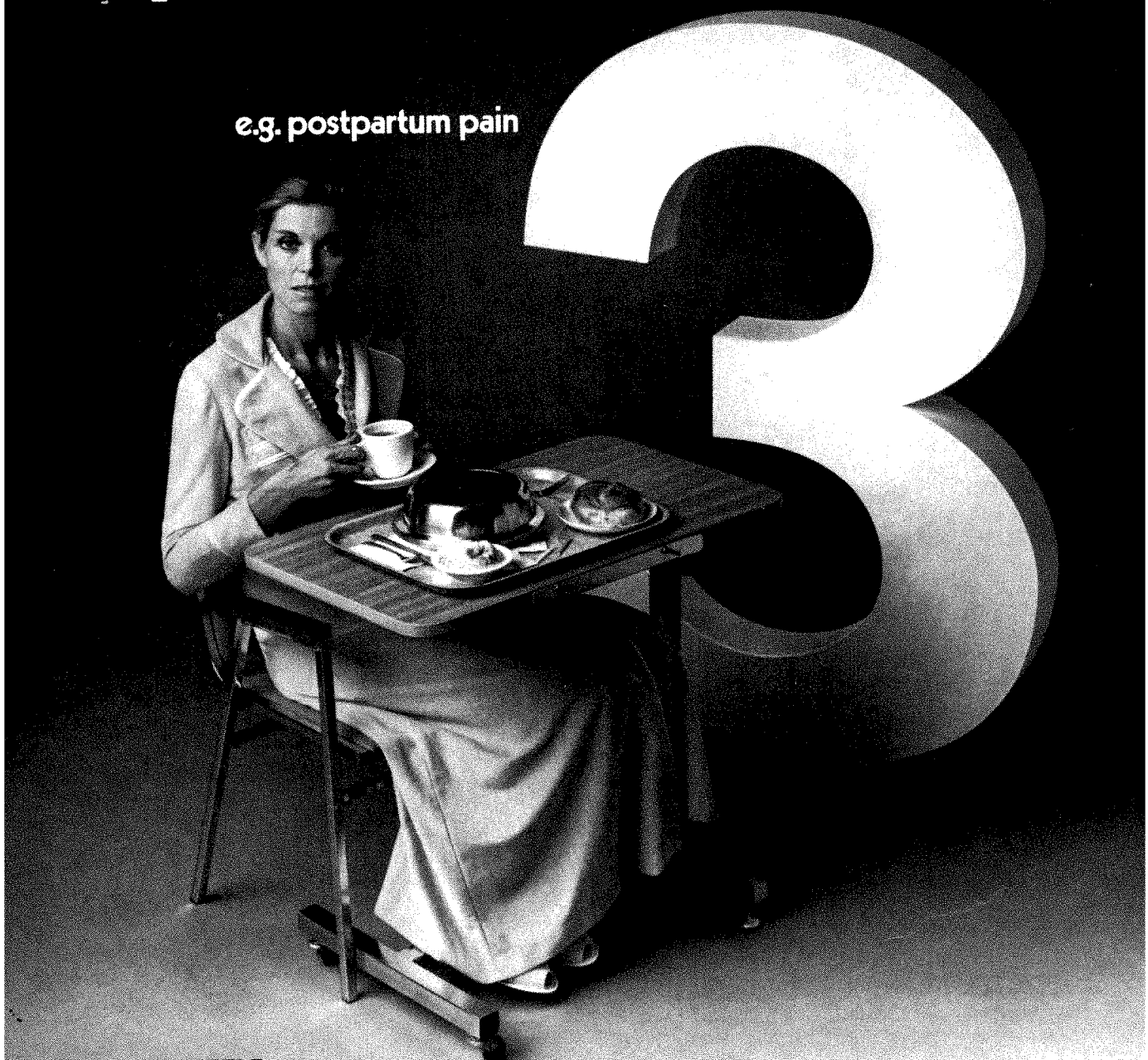
For information on xeroradiography of the breast, write to Xeroradiography, Dept. C, P.O. Box 5786, Pasadena, California 91107.

XEROX

XEROX® is a trademark of XEROX CORPORATION.

No. 3
As potent as the pain it relieves

e.g. postpartum pain



NOT TOO LITTLE
- as potent as the pain you need to relieve in patients with fractures, sprains, strains, wounds, contusions, and the pain of surgical convalescence
- unlike acetaminophen/codeine combinations, it does not sacrifice anti-inflammatory action

NOT TOO MUCH
- potent—yet not excessive
- addiction liability low

NOT TOO EXPENSIVE
- brand-name quality, yet reasonable in cost
- readily available in both hospital and local pharmac

CII CONVENIENCE
- telephone Rx in most states, up to 5 refills in 6 months at your discretion (where state law perm

EMPIRIN® COMPOUND WIT CODEINE NO. 3

codeine phosphate* (32.4 mg) gr ½
Each tablet also contains: aspirin gr 3½, phenacetin gr 2½, caffeine gr ½. *Warning—may be habit-forming.

Wellcome | Burroughs Wellcome
Research Triangle P
North Carolina 2770

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

September 1

1976

Obstetrics

A new approach to patients with suspected anaerobic postpartum pelvic infections. Transabdominal uterine aspiration for culture and metronidazole for treatment 1

William J. Ledger, M.D., Carol L. Gee, M.S., Patricia A. Pollin, M.T., William P. Lewis, Ph.D., Vera L. Sutter, Ph.D., and Sydney M. Finegold, M.D.
Los Angeles, California

Colonic pseudo-obstruction following termination of pregnancy and uterine operation 7

Ian A. Spira, M.B., Ch.B.(Cape Town), F.R.C.S.(Edin.), F.C.S.(South Africa), F.A.C.S., and William I. Wolff, M.D., F.A.C.S.
New York, New York

Primary prostaglandins in amniotic fluid in pregnancy and spontaneous labor 13

F. Dray and R. Frydman
Paris and Clamart, France

(Contents continued on page 7)

Vol. 126, No. 1, September 1, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$37.00	$45.50	$47.00
Personal†	$27.00	$35.50	$37.00
Student, intern, resident†	$21.60	$30.10	$31.60

*(*Postal Union of the Americas and Spain)*

Single copies are $3.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.

Colposcope 9—has ZEISS Quality at Low Price

This corrects the misconception:

that Zeiss Colposcopes are too expensive for use in private practice.

Definitely not Colposcope 9 with its easy fine-focusing device. It was designed, and priced, specifically for use in the office examining room—so that gynecologists can have the same optical excellence and engineering precision in their offices that the clinic demands.

With Colposcope 9, office colposcopy is as affordable as it is necessary for DES detection. And it is advisable in routine examinations, especially in evaluating patients with class 2 pap smears; it helps physicians to better understand early cervical neoplasia, and reduces dramatically the inherent false-negative rate of vaginal sampling.

Three stands—the wall mount that keeps the floor uncluttered; the floor stand, easily movable from room to room; and the convenient mount for the examining table.

Adding accessories is a snap—you can do it in your office.

In contrast to other instruments, there's no need to return Colposcope 9 to have accessories installed.

You'll find the photographic accessories particularly valuable for patient documentation before and after treatment, especially when legal aspects are involved.

Write or call for details or a demonstration.

Nationwide service.

Carl Zeiss, Inc., 444 5th Avenue, New York, N.Y. 10018 (212) 730-4400. Branches in: Atlanta, Boston, Chicago, Columbus, Houston, Los Angeles, San Francisco, Washington, D.C. In Canada: 45 Valleybrook Drive, Don Mills, Ont., M3B 2S6. Or call (416) 449-4660.



Many accessories available:

1. A three-step magnification changer for both viewer and photographic attachments simultaneously.

2. A Polaroid® camera with increased flash power supply for better illumination.

3. A full-frame 35mm camera.

4. The new Zeiss-Urban 35mm split-frame stereo photo adapter for color stereophotographs on one frame in a single exposure.

5. A co-observation tube for viewing the field exactly as the examining physician views it — in both white and red-free light.

Contents continued from page 5

Asymptomatic bacteriuria in pregnancy: Antibody-coated bacteria, renal function, and intrauterine growth retardation 20
Robert E. Harris, M.D., Ph.D., Virginia L. Thomas, Ph.D., and Alexis Shelokov, M.D.
Lackland Air Force Base and San Antonio, Texas

Systolic time intervals in normotensive and hypertensive human pregnancy 26
Y. L. Lim, B.Med.Sc., M.B., B.S., and W. A. W. Walters, M.B., B.S., Ph.D., F.R.C.O.G., F.A.G.O.
Melbourne, Victoria, Australia

The relationship of hospital-acquired maternal infection to invasive intrapartum monitoring techniques 33
Charles B. Gassner, M.D., and William J. Ledger, M.D., F.A.C.O.G.
Los Angeles, California

Renal clearances of estriol conjugates in normal human pregnancy at term 38
Bruce K. Young, M.D., Helmut Jirku, Ph.D., Susan Kadner, B.S., and Mortimer Levitz, Ph.D.
New York, New York

Neonatal respiratory distress following elective delivery. A preventable disease? 43
Maureen Hack, M.B.Ch.B., Avroy A. Fanaroff, M.B., M.R.C.P.E., Marshall H. Klaus, M.D., Barry D. Mendelawitz, M.B., M.R.C.O.G., and Irwin R. Merkatz, M.D.
Cleveland, Ohio

The response of the human Fallopian tube to ergonovine and methyl-ergonovine in vivo 48
Elsimar M. Coutinho, M.D., Hugo Maia, M.D., and Lusia Nascimento, M.D.
Salvador, Bahia, Brazil

Suboptimal pregnancy outcome among women with prior abortions and premature births 55
Steve J. Funderburk, M.D., Donald Guthrie, Ph.D., and David Meldrum, M.D.
Los Angeles, California

Fetus, placenta, and newborn

Antepartum fetal heart rate and uterine activity studies. I. Preliminary report of accelerations and the oxytocin challenge test 61
H. E. Fox, M.D., M. Steinbrecher, B.S., and B. Ripton, B.S.N.
Rochester, New York

Classification of human fetal movement 70
Ilan Timor-Tritsch, M.D., Ivan Zador, M.Sc., Roger H. Hertz, M.D., and Mortimer G. Rosen, M.D.
Cleveland, Ohio

(Contents continued on page 9)

The causes of vaginitis are multiple



You can depend on AVC... therapy that combats major vaginal pathogens and provides rapid symptomatic relief.*

***Indications:** Based on a review of AVC by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually *Trichomonas vaginalis*, *Candida albicans*, or *Hemophilus vaginalis*) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Known sensitivity to sulfonamides.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.

Dosage: 1 applicatorful (about 6 g.) or 1 suppository intravaginally once or twice daily.

Supplied: Cream–4 ounce tube with applicator. Suppositories–Box of 16 with inserter.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

4-6744 (6049)

The treatment is singular

AVC™

Cream (aminacrine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%)

Suppositories (aminacrine hydrochloride 0.014 g., sulfanilamide 1.05 g., allantoin 0.14 g.)

Contents continued from page 7

Respiratory distress syndrome with mature lecithin/sphingomyelin ratios: Diabetes mellitus and low Apgar scores 78
A. C. Cruz, M.D., W. C. Buhi, M.S., S. A. Birk, R.N., and W. N. Spellacy, M.D.
Gainesville, Florida

Reported live births following induced abortion: Two and one-half years' experience in Upstate New York 83
George Stroh and Alan R. Hinman, M.D.
Albany, New York

Gynecology

Ovarian morphology in women with anosmia and hypogonadotropic hypogonadism 91
R. L. Goldenberg, R. D. Powell, Saul W. Rosen, John R. Marshall, and G. T. Ross
Bethesda, Maryland

Excision of submucus fibroids with hysteroscopic control 95
Robert S. Neuwirth, M.D., and Hussein K. Amin, M.D.
New York, New York

Antibodies to adeno-associated satellite virus and herpes simplex in sera from cancer patients and normal adults 100
Heather D. Mayor, Stephanie Drake, Joyce Stahmann, and David M. Mumford
Houston, Texas

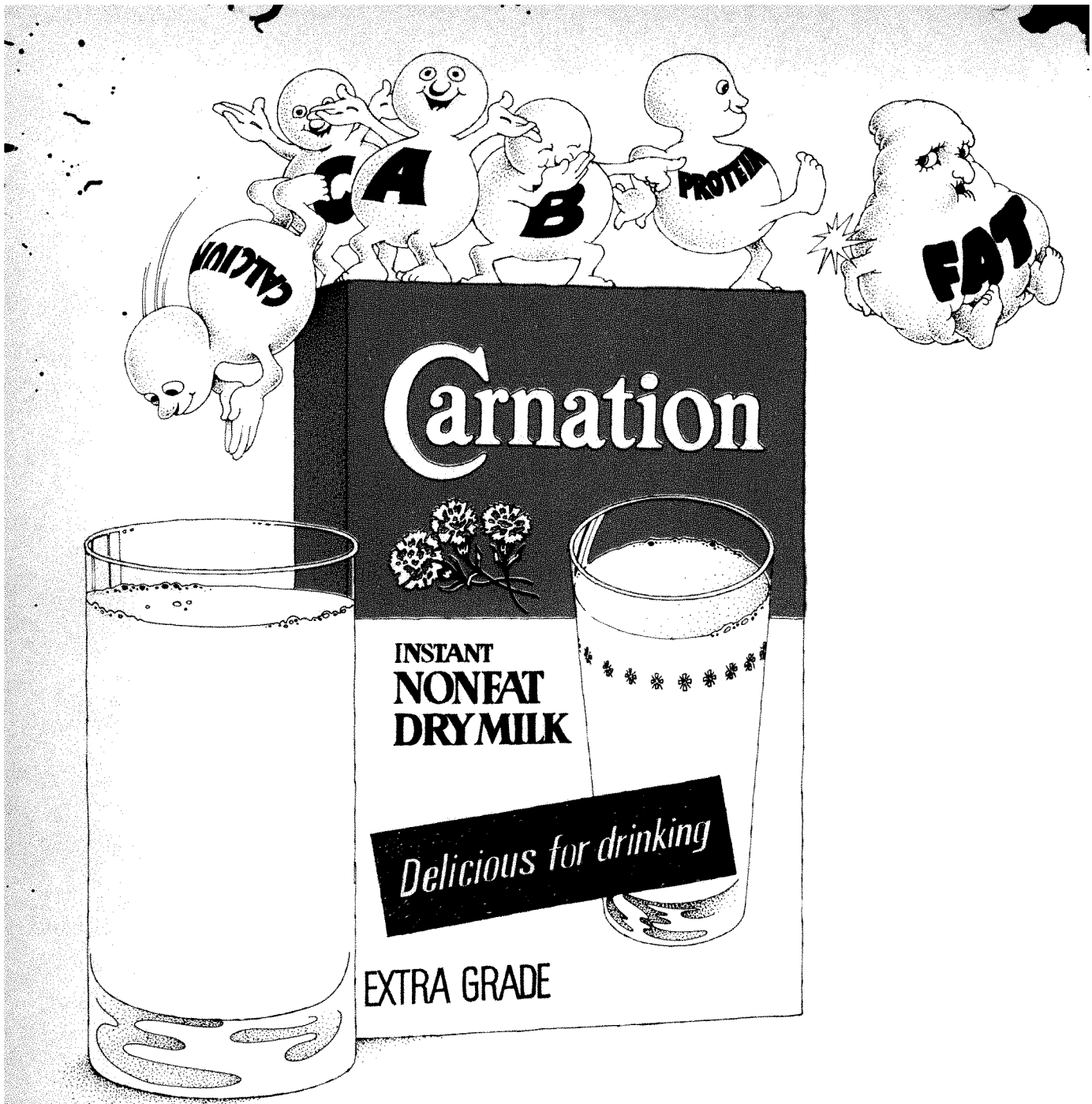
Carcinoembryonic antigen in intraepithelial neoplasia of the uterine cervix 105
J. R. van Nagell, Jr., M.D., W. R. Meeker, M.D., J. C. Parker, Jr., M.D., Rafiah Kashmiri, M.S., and Viola McCollum, B.A.
Lexington, Kentucky

A hypothesis: The role of a high-risk male in the etiology of cervical carcinoma 111
Albert Singer, Ph.D.(Syd.), D.Phil.(Oxon), M.R.C.O.G., Bevan L. Reid, M.D., B.V.Sc., and Malcolm Coppleson, M.D., F.R.C.O.G.
Sheffield and Birmingham, England, and Sydney, Australia

Circulatory and cellular immune responses to squamous cell carcinoma of the uterine cervix 116
Wen Tsuo Chiang, Ping Yen Wei, and E. Russell Alexander
Seattle, Washington

Outpatient evaluation of patients with atypical Papanicolaou smears: Contribution of endocervical curettage 122
Hugh M. Shingleton, M.D., Hazel Gore, M.B., B.S., and J. Max Austin, Jr., M.D.
Birmingham, Alabama

(Contents continued on page 11)



We've got all of the good guys and none of the bad guys.

Carnation Instant Nonfat Dry Milk has taken all the good parts of whole milk like protein, calcium, and B-vitamins—and has eliminated the bad...like fat.

In addition, Carnation Instant Nonfat Dry Milk is fortified with vitamins A and D. And since it starts out dry, you can control the balance of protein and solids to suit any low-fat diet.

We even have these free diet plans to make things better:

1. Reducing
2. Pregnancy Weight Control
3. Low Sodium
4. Cholesterol Control for Weight Reduction
5. Cholesterol Control for Normal Weight Patients
6. Diabetic
7. Bland Ulcer

We can't think of a reason not to prescribe Carnation Instant Nonfat Dry Milk to all of your patients.

For a free supply of any of tl diet plans listed, circle the corr sponding number(s): 1, 2, 3, 4, 5, 6,

Send this completed coupon tc Carnation Company, P.O. Box 550 Dept. **6B3,** Pico Rivera, Calif. 90665

Name_____

Address_____

City_____

State_____ Zip_____

Contents continued from page 9

Volatile constituents of human vaginal secretions 129
George R. Huggins, M.D., and George Preti, Ph.D.
Philadelphia, Pennsylvania

Current investigation

Placental prostaglandin levels in pre-eclampsia 137
Laurence M. Demers, Ph.D., and Steven G. Gabbe, M.D.
Hershey, Pennsylvania, and Los Angeles, California

Classic pages

Classic pages 140

Current developments

Oral contraceptive–induced hypertension—Nine years later 141
John H. Laragh, M.D.
New York, New York

Items

Items 148

(Information for authors on page 21)

ANTISEPTIC SECURITY

in Ob/Gyn practice

Prompt, broad-spectrum action of BETADINE Microbicides provides topical antiseptic security for patients, physicians and nurses

BETADINE Solution Microbicidal Applicator, the only 8½" long, disposable antiseptic-impregnated swabstick, is indicated for degerming hard-to-reach sites, such as the cervix, vulvovaginal, perineal and anorectal areas

BETADINE Solution, for prepping skin, vagina and perineum, and for general antiseptic use on skin, mucosa and wounds

BETADINE Surgical Scrub, for preoperative scrubbing and for hand and skin degerming (In the rare instance of local irritation or sensitivity, discontinue use in the individual)

BETADINE Douche, for treating vaginal moniliasis, *T. vaginalis* vaginitis and nonspecific infectious vaginitis (*H. vaginalis* vaginitis)... also ideal for routine cleansing, due to its degerming and deodorizing properties

Purdue Frederick

© COPYRIGHT 1975, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A8076 168875



BETADINE® Microbicides

Foremost documented broad-spectrum topical microbicides



Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

Advisory committee on policy

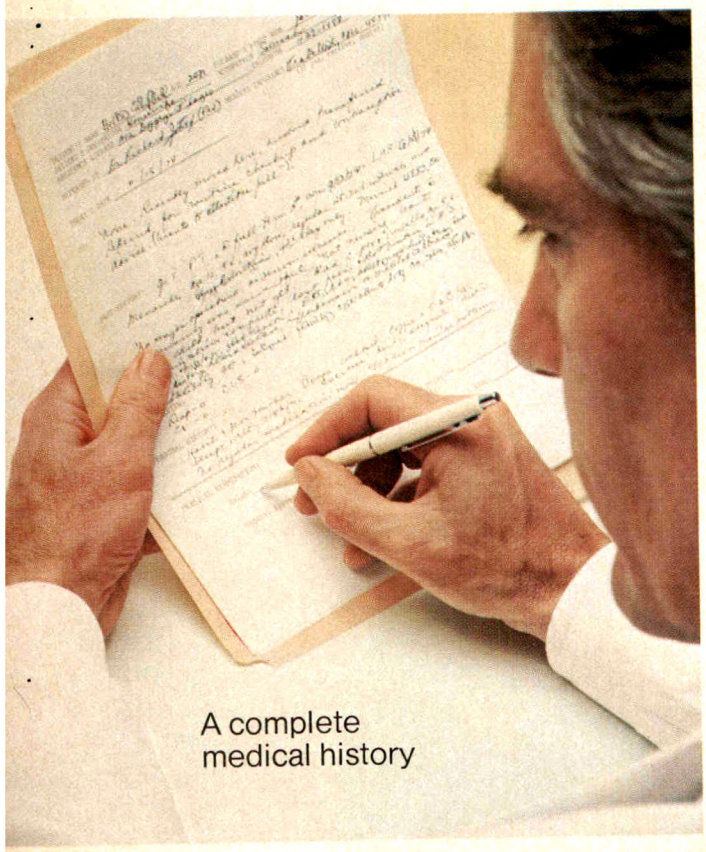
David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

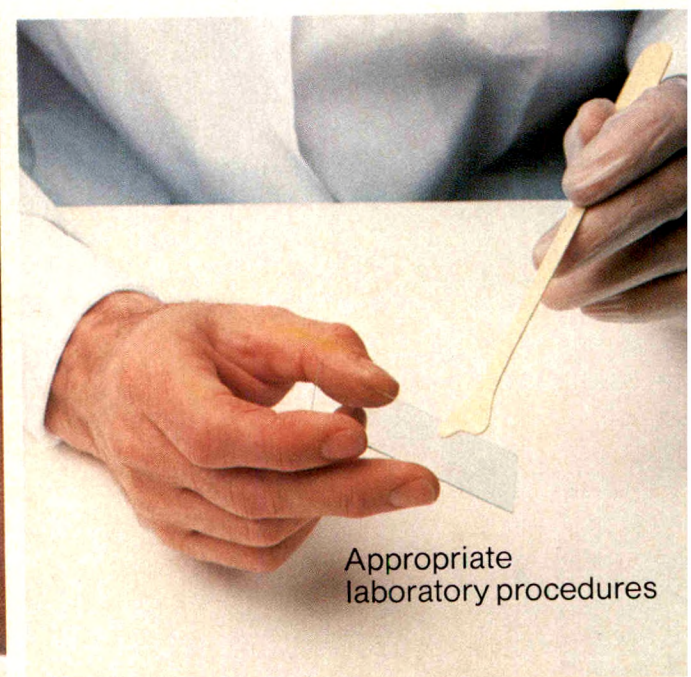
Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*

Prudent Practice...

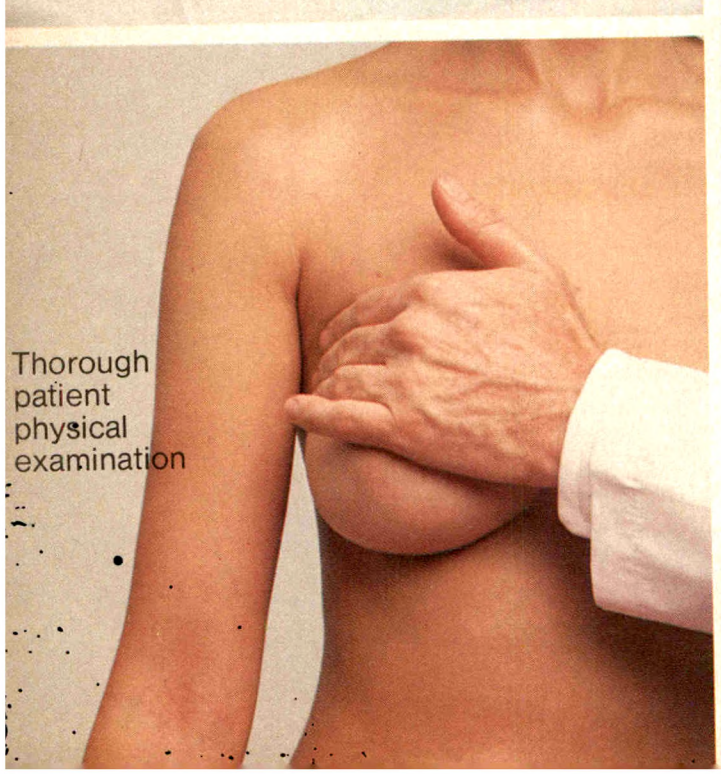
Some sensible steps physicians take before prescribing an oral contraceptive



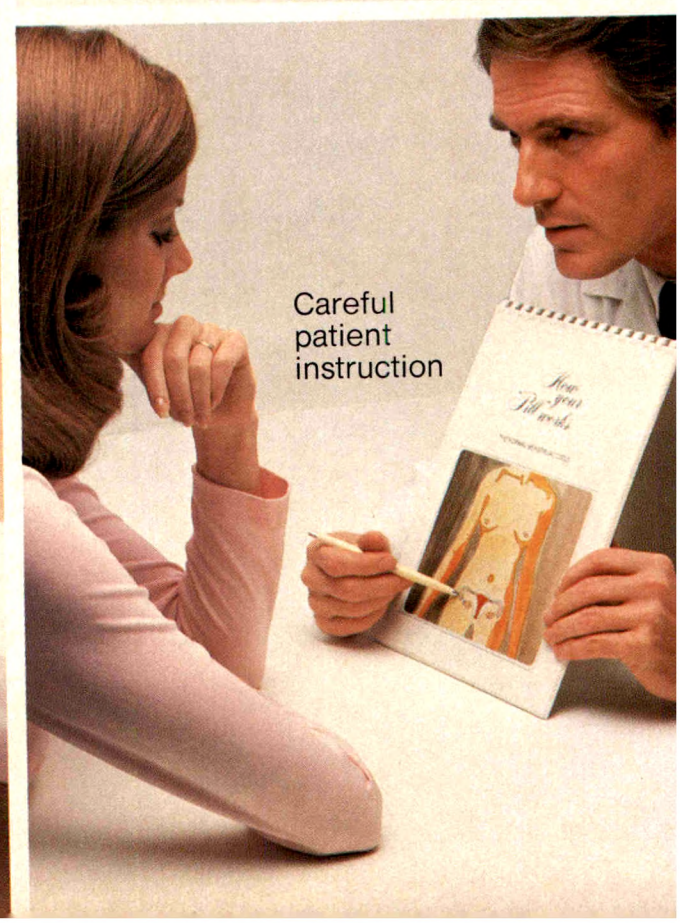
A complete medical history



Appropriate laboratory procedures



Thorough patient physical examination



Careful patient instruction

And when you prescribe a combination oral contraceptive, it's also prudent practice to employ the lowest effective dose of estrogen that is otherwise acceptable.

For many women, this could mean Loestrin 1/20—20 mcg of ethinyl estradiol in combination with 1 mg of norethindrone acetate.

As you would expect, irregular bleeding and occasionally the absence of bleeding, especially during the first few cycles, are more frequent with Loestrin 1/20 than with combinations containing larger doses of estrogen. Nevertheless, clinical trials demonstrated that more than 85% of the subjects, some of whom experienced such irregular cycles, found Loestrin 1/20 an acceptable oral contraceptive.

Effective contraception... with a low dose of estrogen—a tough combination to beat.

The lowest dose of a proven effective estrogen in a combination oral contraceptive

LOESTRIN® 1/20

Each white tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each brown tablet contains 75 mg ferrous fumarate, USP.

PARKE-DAVIS



And with the Pill...

"...it would appear prudent to limit estrogen exposure to that amount which will successfully fulfill the purpose for which oral contraceptives were devised, namely, to prevent conception."* Hence, good therapeutics would indicate the lowest effective dose of estrogen that is otherwise acceptable.

*Preston S N: Contraception 6:17 (July) 1972.

See next page for prescribing information.

LOESTRIN 1/20

Each white tablet contains:
norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate) . . . 1 mg
ethinyl estradiol (17 alpha-ethinyl-1,3,5 (10)-estratriene-3, 17 beta-diol) . . . . . 20 mcg
Each brown tablet contains
75 mg ferrous fumarate, USP

BRIEF SUMMARY OF PRESCRIBING INFORMATION

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of Loestrin 1/20 is somewhat lower than that of the higher-dose combination products. Both provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials that were conducted with Loestrin 1/20, appears to be somewhat higher than observed with higher-dose combination products. This higher dropout rate was observed to be due particularly to irregular bleeding.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

Loestrin 1/20 is indicated for the control of conception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of Loestrin 1/20 in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

2. Endocrine and possibly liver function tests may be affected by treatment with Loestrin 1/20. Therefore, if such tests are abnormal in a patient taking Loestrin 1/20, it is recommended that they be repeated after the drug has been withdrawn for two months.

3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. An alteration in menstrual patterns in many patients is likely to be induced by using Loestrin 1/20. The amount and duration of flow and cycle length may be variable. Because of these irregular bleeding patterns, it is important that the physician take this into consideration when attempting to determine if persistent bleeding is from organic causes.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged Loestrin 1/20 therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Loestrin 1/20 therapy.

9. The age of the patient constitutes no absolute limiting factor, although treatment with Loestrin 1/20 may mask the onset of the climacteric.

10. The pathologist should be advised of Loestrin 1/20 therapy when relevant specimens are submitted.

11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Cerebral thrombosis
Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, e g, retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea during and after treatment
Edema
Chloasma or melasma
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)
Changes in cervical erosion and cervical secretions
Suppression of lactation when given immediately postpartum
Cholestatic jaundice
Migraine
Rash (Allergic)
Rise in blood pressure in susceptible individuals
Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post treatment
Premenstrual-like syndrome
Changes in libido
Changes in appetite
Cystitis-like syndrome
Headache
Nervousness
Dizziness
Fatigue
Backache
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: increased sulfobromophthalein retention and other tests

Coagulation tests: increase in prothrombin, factors VII, VIII, IX, and X.

Thyroid function: increase in PBI and butanol extractable protein-bound iodine, and decrease in T^3 uptake values

Metyrapone test

Pregnanediol determination

DOSAGE AND ADMINISTRATION

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown tablets have been started. Because of the relatively low estrogenic content, Loestrin 1/20 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen to achieve cyclic regularity than that contained in Loestrin 1/20. These patients experience altered bleeding patterns, which do not conform to treatment schedules, while taking the white Loestrin 1/20 tablets. However, it is important that patients adhere to the dosage schedule regardless of when bleeding occurs.

The occurrence of altered bleeding is highest in Cycle 1. The majority of patients will have seven days or less of total bleeding during the 28-day cycle (including both withdrawal bleeding and breakthrough bleeding and spotting). Should irregular bleeding occur, patients should be reassured and instructed to continue taking the tablets as directed. If by the third cycle the irregular patterns are unacceptable, consideration should be given to changing the medication to a product with higher estrogen content (Norlestrin®-1 mg or Norlestrin-2.5 mg). The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic causes, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

SE

1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. *J Coll Gen Pract* 13:267-279, 1967.
2. Inman W H W and Vessey M P: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. *Br Med J* 2:193-199, 1968.
3. Vessey M P and Doll R: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. *Br Med J* 2:651-657, 1969.
4. Sartwell P E, Masi A T, Arthes F G, Greene G R and Smith H E: Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. *Am J Epidemiol* 90:365-380, 1969.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

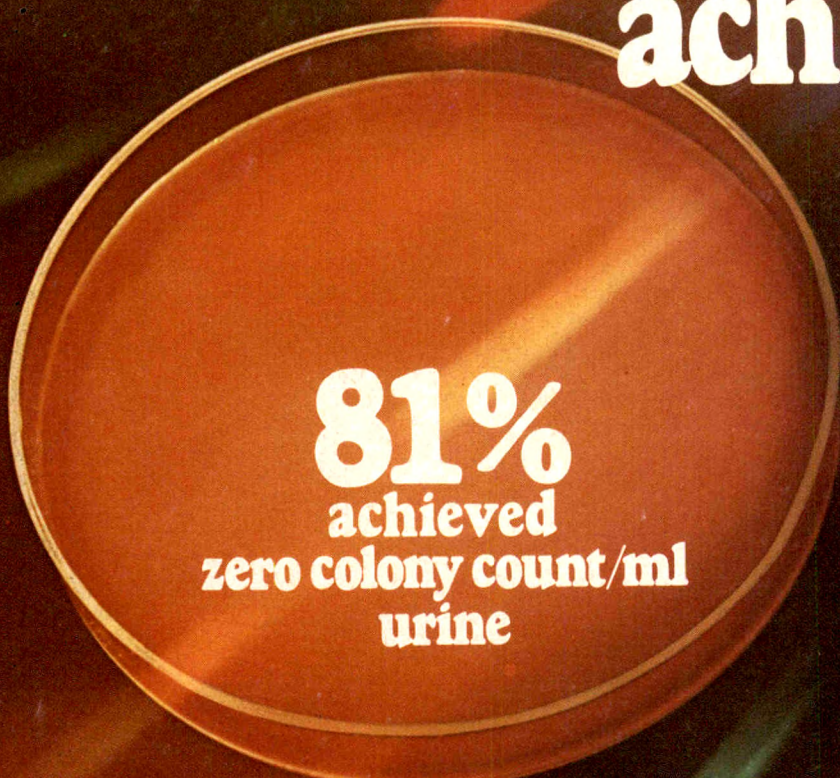
PD-JA-1388-2-P (8-75)

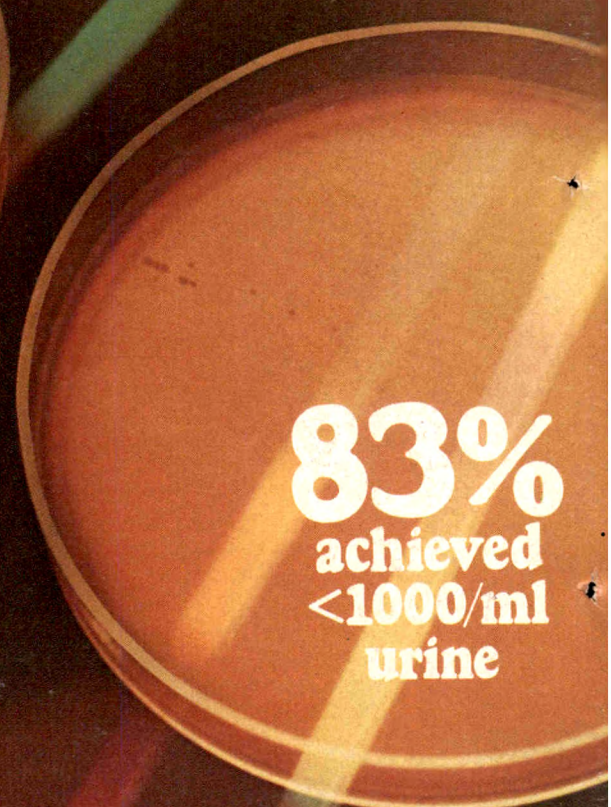
American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS
AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY

However you define in acute cystitis achieved an





*In a new study 8 out of 10 patients with acute lower urinary tract infection, primarily cystitis, achieved sterile urine. All infections were nonobstructed. Susceptible organisms included *E. coli*, *Klebsiella-Aerobacter*, *Proteus mirabilis* and *Proteus vulgaris*.

No. of patients	Sterile urine	Clear culture <1000 organisms/ml urine	Clear culture <10,000 organisms/ml urine
406	81% (330)	83% (339)	88% (357)

Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey

clear culture

Gantanol® B.I.D.
(sulfamethoxazole)

81% to 88% cure rate*



Gantanol® B.I.D.
sulfamethoxazole/Roche

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

Basic therapy with convenience and economy in acute nonobstructed cystitis†

†due to susceptible organisms

Please see following page for summary of product information.

ROCHE

Gantanol® B.I.D.

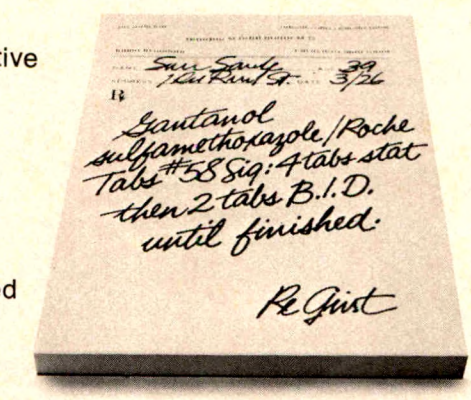
sulfamethoxazole/Roche

Basic therapy with convenience and economy in acute nonobstructed cystitis*

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

- ☐ Effective in nonobstructed cystitis.
- ☐ Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- ☐ Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- ☐ Convenient, economical B.I.D. dosage.
- ☐ Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- ☐ As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.

*due to susceptible organisms



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.* **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

P24,263

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2*, Current Investigation and Clinical Opinion, limited to *6*, and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials

Cycle	1	12	24	36	Total Cycles 20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN•BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll. R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. *3*:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 1 SEPTEMBER 1, 1976

OBSTETRICS

A new approach to patients with suspected anaerobic postpartum pelvic infections. Transabdominal uterine aspiration for culture and metronidazole for treatment

WILLIAM J. LEDGER, M.D.
CAROL L. GEE, M.S.
PATRICIA A. POLLIN, M.T.
WILLIAM P. LEWIS, PH.D.
VERA L. SUTTER, PH.D.
SYDNEY M. FINEGOLD, M.D.
Los Angeles, California

Oral metronidazole was given as therapy in 25 women with the clinical diagnosis of a postpartum anaerobic soft tissue pelvic infection following a vaginal delivery. There was a good clinical response in 80 per cent of these women. No anaerobic organisms resistant to metronidazole were recovered in the treatment failures. Different specimen collection techniques were evaluated, with anaerobes recovered in 4 per cent of the blood cultures, 26.3 per cent of the transabdominal endometrial aspirations, and 88 per cent of the transcervical endometrial samples. The aerobic recovery of organisms was 4 per cent from blood cultures, 15.8 per cent from transabdominal endometrial aspirations, and 96 per cent from the transcervical approach. The significance of these findings is discussed.

From the Departments of Obstetrics and Gynecology and Pathology, the University of Southern California School of Medicine; Infectious Disease Section, Wadsworth Hospital Center; Department of Medicine, University of California, School of Medicine.

Supported by a grant from G. D. Searle and Company.

Received for publication October 7, 1975.

Accepted January 22, 1976.

Reprint requests: William J. Ledger, M.D., Women's Hospital, LAC-USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033.

RECENTLY, THERE has been increasing interest in anaerobic organisms in pelvic infections. In patients with soft tissue infections, Gorbach and Thadepalli[1] have documented a high percentage of cultures positive for anaerobes and have shown clinical effectiveness with antibiotics effective against anaerobes. In an attempt to delineate the importance of anaerobic organisms in postpartum pelvic infections, metronidazole, an agent whose antibacterial activity is limited to anaerobic organisms, was used in this clinical

Table I. Pretreatment recovery of anaerobic and aerobic organisms by route of specimen collection

Transcervical endometrial cultures	*Transabdominal endometrial cultures*	*Blood cultures*
Anaerobes:		
22 of 25 (88%) were positive	5 of 19 (26.3%) were positive	1 of 25 (4%) was positive
50 different organisms recovered	7 different organisms recovered	One organism recovered
Aerobes:		
24 of 25 (96%) were positive	3 of 19 (15.8%) were positive*	1 of 25 (4%) was positive
50 different organisms recovered	4 different organisms recovered	One organism recovered

*Only one positive when no anaerobes were recovered.

trial. In additiom to the traditional collection techniques of transcervical endometrial specimens and blood cultures, transabdominal endometrial aspiration was studied.

Materials and methods

Twenty-five febrile postpartum women following a vaginal delivery were evaluated. All 25 had the clinical diagnosis of an anaerobic endomyometritis, based upon the presence of fever, uterine tenderness on abdominal and pelvic examination, and a foul-smelling lochia. In addition, two patients were thought to have more extensive soft tissue pelvic infections, secondary to prior pudendal and paracervical anesthesia, because of their inability to bear weight or to tolerate any hip joint movement. All patients were informed of the experimental nature of the use of metronidazole in this context and agreed to participate in the study. They were given metronidazole, 250 mg. orally, every 6 hours for 10 days. Twenty of these 25 women with an endomyometritis were treated initially with metronidazole and five were given this drug when they remained febrile after exposure to other antibiotics for their endomyometritis.

The 25 women in this study ranged in age from 19 to 32 years, with the mean age of 24.4 years and a median age of 25 years. Twelve of these 25 patients were primigravidas and 24 were Mexican-American. All patients delivered vaginally, with 14 having a spontaneous delivery, seven by outlet or low forceps, and four by vacuum extraction.

All 25 women were asked for permission to attempt a transabdominal endometrial aspiration for culture as well as the traditional transcervical endometrial culture and the blood culture. Only 20 women were willing to accept this new diagnostic procedure. In these 20 women, the lower abdomen was mechanically cleansed and then sprayed with a 1 per cent Betadine solution. After this had dried, the skin below the umbilicus in the midline was infiltrated with 1 per cent xylocaine. The uterus was entered through the abdominal wall in one thrust with a No. 18 spinal needle. In one patient, urine was obtained on aspiration and this diagnostic attempt was terminated. In the other 19 women, usually less than 1 c.c. of bloody material was obtained by aspiration with a 10 c.c. syringe. The needle was changed and the material was injected into a tube with 10 c.c. of thioglycollate broth with 1.0 c.c. of Bacto Fildes extract added. Approximately 0.5 c.c. of the broth was reaspirated into the syringe and a drop was plated within 5 minutes on reduced plates of Brucella manadione blood agar and laked Brucella agar plates with 7.5 μg per milliliter of vancomycin, 75 μg per milliliter of kanamycin, and 0.5 μg per milliliter of menadione added. The standard endometrial cultures were obtained on all 25 women with a transcervical approach utilizing swabs, which were placed in a similar thioglycollate tube or streaked on reduced media plates. Both sets of specimens were placed into a Gas Pak jar, which was activated and incubated. Ten c.c. of blood were obtained for culture and 5 c.c. were inoculated in each of two bottles containing 100 c.c. of tryptose phosphate broth. A repeat transcervical endometrial culture was obtained 2 to 3 days after initiation of therapy. In those patients with a satisfactory response to metronidazole, this occurred when these women had been afebrile for 24 hours or more. In those patients with a failure of therapeutic response, the repeat culture was obtained while they were febrile. All cultures were observed for a minimum of 10 days before being reported as having no anaerobic growth.

In the LAC-USC anaerobic laboratory, initial identification of anaerobic isolates was made on the basis of colony morphology, microscopic characteristics, and the antibiotic disc identification procedure suggested by Sutter, and co-workers.[2] All anaerobic isolates were transported to the Wadsworth Anaerobic Bacteriology Laboratory, to be identified by previous published criteria and to have agar dilution testing performed for susceptibility to metronidazole.

Results

The pretreatment recovery of aerobic and anaerobic organisms by various culture routes is noted in Table I. The transcervical route had both the highest yield of positive cultures and the most isolates, with the mean of four per patient sampled. The transabdominal route had positive bacterial growth in seven of 19 women sampled (36.8 per cent). The pretreatment anaerobic isolates are listed in Table II. Bacteroides species were the single most common isolate. The pretreatment aerobic isolates are listed in Table III.

Table II. Pretreatment anaerobic isolates

Transcervical endometrial cultures (50 isolates)	*Transabdominal endometrial cultures (7 isolates)*	*Blood cultures (1 isolate)*
Gram-positive:	*Gram-positive:*	*Gram-negative:*
1. Cocci—	1. Cocci—	1. Rod—
Peptococcus asaccharolyticus—4	Peptococcus sp.—1*	Bacteroides sp.
Peptococcus prevotii—2		
Peptococcus variabilis—2	2. Bacilli—	
Peptococcus magnus—1	*Propionibacterium acnes*—1	
Peptococcus sp.—2*		
Peptostreptococcus anaerobicus—6		
Microaerophilic strep.—2		
2. Bacilli—		
Clostridium perfringens—2		
Propionibacterium acnes—1		
Lactobacillus acidophilus—1		
Unidentified non-spore-forming—1*		
Gram-negative:	*Gram-negative:*	
1. Cocci—	1. Cocci	
Veillonella parvula	*Veillonella parvula*—1	
2. Rods–	2. Rods	
Bacteroides sp.—12	Bacteroides species—3	
B. fragilis ss. fragilis—2	Gram-negative rod—1*	
B. fragilis ss. thetaiotacmicron—1		
B. fragilis, other—1		
B. melaninogenicus ss. *intermedius*—2		
B. melaninogenicus ss. *asaccharolyticus*—1		
B. melaninogenicus, other—2		
B. oralis—1		
Fusobacterium nucleatum—1		
F. gonidiaformans—1		

*Growth not sustained for subsequent biochemical identification.

Fifteen of these 25 women met the standard temperature definition of postpartum febrile morbidity. Twenty of the 25 patients had a successful clinical response to metronidazole as judged by the resolution of fever and disappearance of clinical symptomatology. Five women remained febrile after initiation of the metronidazole therapy and required additional antibiotics before they were considered cured. The mean fever indices of the patients whose metronidazole therapy was judged a success or failure are noted in Table IV. There is no statistically significant difference between the pretreatment fever indices of the two groups. The posttreatment fever index in the patients with a clinical cure is significantly lower than in the regimen failures ($p < 0.01$). A detailed analysis of the five treatment failures is noted in Table V. In one patient with an *E. coli* bacteremia, no anaerobes were isolated. In the other four patients in whom both aerobes and anaerobes were recovered on the pretreatment cultures, none of the anaerobes was resistant to metronidazole in the laboratory and in only one case were anaerobes recovered from treatment cultures.

Comment

Any microbiologic evaluation of the significance of anaerobic organisms in soft tissue pelvic infections is difficult because of the abundant anaerobic flora in adjacent mucous membranes, particularly the vagina and endocervix. The underlying question in every reported study is the impact of contamination upon the observed microbiologic results. Many investigators have demonstrated that anaerobic organisms can be recovered from the endocervix and vaginal surface of at least 70 per cent of patients. In the present study, anaerobes were recovered in 22 of 25 patients or in 88 per cent of the transcervical endometrial cultures. A wide variety of anaerobes was seen with Bacteroides species the most common anaerobic isolate. Anaerobic organisms were not eliminated after 2 to 3 days of metronidazole therapy for anaerobes were still recov-

Table III. Pretreatment aerobic isolates

Transcervical endometrial cultures (50 Isolates)	*Transabdominal endometrial cultures (4 Isolates)*	*Blood cultures (1 isolate)*
Gram-positive:	*Gram-positive:*	*Gram-negative:*
1. Cocci—	1. Cocci—	1. Rods
Enterococcus—11	Coag.neg. staph.—2	*E. coli*—1
Coagulase-negative staphylococcus—9	2. Enterococcus—1	
Streptococcus viridans–3	3. Bacilli— Diphtheroid—1	
Beta strep, not A or D—2		
2. Bacilli Diphtheroids—9		
Gram-negative:		
E. coli—13		
Proteus—2		
Other:		
Candida—1		

Table IV. The mean fever index of patients receiving metronidazole for a suspected anaerobic endomyometritis

	Successful (N = 20) (degree-hours)	*Unsuccessful (N = 5) (degree-hours)*	*Differences*
Pretreatment ± S.E.	35.2 ± 7.3	46.3 ± 18.0	N.S.
Posttreatment ± S.E.	16.8 ± 2.4	89.3 ± 19.6	$P < 0.01$
Total	52.0	135.6	

ered in 14 of 25 samples obtained during treatment or 56 per cent.

To avoid the anaerobic bacterial contamination of the lower genital tract, a new transabdominal approach to endometrial specimen collection was attempted in this study. All were done by one investigator (W. J. L.). The technique was free of serious complications for there were not intra-abdominal or intrauterine bleeding episodes noted. There were no problems with the patient whose bladder was inadvertently entered. This was not surprising, for this is an accepted diagnostic technique for evaluating the urinary tract. Most patients reported less discomfort with this abdominal sampling procedure than with blood culture collection. A major problem with the technique is the paucity of material obtained for culture and the constant concern that the endometrial cavity has not been sampled. In every instance, the material obtained was insufficient for primary inoculation on the plates. Despite this, bacterial growth was present in six of 19 (36.8 per cent) of the samples. This technique represents a significant improvement in the incidence of positive cultures, when compared to the blood culture. Further investigation is indicated to see if it is a practical alternative method to the blood culture for obtaining a noncontaminated sample of potential pathogens in patients with a postpartum endomyometritis. Whether the failure to recover anaerobes by transabdominal aspiration represents the true microbiologic status of the endometrial cavity of the patient with a postpartum endomyometritis or is simply a failure of the technique to sample this area cannot be judged by this study, but clinically all of the patients had anaerobic infections.

The clinical and microbiological data in this preliminary evaluation suggest that metronidazole is an effective agent in the treatment of anaerobic soft tissue pelvic infections. There was a successful clinical response in 20 of the 25 patients (80 per cent) with endomyometritis and a foul-smelling lochia with a mean postmetronidazole treatment fever index of 16.8 degree-hours. This is significantly less posttreatment fever than seen in the therapy failures of 89.3 hours (see Table II), and can be compared to the mean posttreatment fever index in 13 patients in a previous fever index evaluation of endometritis of 68.5 degree-hours.[3] Aerobes were also recovered by transcervical endometrial cultures. If these aerobic isolates are not contaminants, the patients successfully treated with metronidazole alone confirm the observations of Gorbach and Thadepalli,[1] that incomplete antibacterial coverage in mixed soft tissue pelvic infections frequently result in a clinical cure. The frequent recovery of aerobes would suggest that antibiotics effective against these organisms might be combined with metronidazole in more acutely ill patients. The frequent recovery of anaerobes (65 per cent) in afebrile patients who are successfully responding to medication may indicate only residual normal flora, particularly since they had been treated for only 2 to 3 days when these cultures were obtained. Of the five patients who failed to respond to metronidazole, and remained febrile, none of the anaerobes recovered on pretreatment culture was resistant to metronidazole. In addition, only one anaerobe was recovered on later culture and this was again susceptible to metronidazole. This indicates that metronidazole resistant anaerobes were not the cause of these treatment failures and suggests that aerobic organisms were the source of these failed therapies.

In addition to these results, there were individual observations that suggested the clinical effectiveness of metronidazole. Both of the women with extensive soft tissue pelvic infections had a dramatic response to this drug. They were both able to bear weight within 24 hours of the initiation of therapy and rapidly became afebrile. These patients have previously been noted on our service to have a more protracted convalescence.

Table V. Analysis of treatment failures

Pre-treatment culture source	*Organisms*	*During treatment culture source*	*Organisms*	*Additional therapy and outcome*
Transcervical blood	*E. coli* *E. coli*	Transcervical	No growth	Kanamycin cure
Transcervical	*B. fragilis* *E. coli* Enterococcus *Streptococcus viridans* Diphtheroid	Transcervical	*B. fragilis* *E. coli* Enterococcus	Ampicillin cure
Transcervical	*C. perfringens* *E. coli* Enterococcus	Transcervical	*E. coli*	Penicillin and kanamycin cure
Transcervical	*B malaninogenicus* ss. *intermedius* *Microaerophilis strep.* *E. coli*	Transcervical	No growth	Kanamycin cure
Transcervical	Bacteroides sp. *Peptococcus asaccharolyticus* Enterococcus Diphtheroid Coag.-neg. staph.	Transcervical	*E. coli* Enterococcus Diphtheroid Coag.-neg. staph.	Ampicillin cure
Transabdominal	Peptococcus			

The present availability of only the oral form of metronidazole limits its clinical application. In the present study, the administration of this drug was restricted to that group of obstetric-gynecologic patients with the least severe anaerobic soft tissue pelvic infections, i.e., those women who delivered vaginally, and subsequently developed a postpartum endomyometritis. A past evaluation of the absorption of 250 mg. of oral metronidazole in five healthy normal male volunteers demonstrated a mean peak serum level of 6.23 μg per milliliter or greater, with a mean serum half-life of 8.24 hours.[4] These levels exceed the minimal inhibitory concentration of most anaerobic organisms. In this study, only three of 50 anaerobic pretreatment isolates had MIC's of greater than 8 μg per milliliter. All three were isolated from women who had a successful clinical response to metronidazole. Two of the resistant isolates were gram-positive, non–spore-forming rods which have questionable pathogenicity. Another was a Bacteroides species with an MIC greater than 128 μg per milliliter; despite this, the patient had a rapid clinical response while on the drug. The significance of this observation is not known. It may represent contamination or the importance of host-defense mechanisms in young healthy women. The absorption of metronidazole in febrile postpartum patients and the delivery to the endometrial cavity has not been evaluated. In critically ill patients with serious soft tissue pelvic infections, there would be concern about the absorption of this oral medication. Until a parenteral form of medication is available, it is unlikely that there will be any widespread testing of the efficacy of metronidazole in women with serious anaerobic soft-tissue pelvic infection.

The exact place of this medication in the treatment of anaerobic soft tissue pelvic infections in obstetrics and gynecology will be dependent upon many factors. This medication needs to be compared with currently employed antibiotics to determine relative efficacy. In addition, recent laboratory investigations suggest that metronidazole is carcinogenic to mice.[5] It should be noted that INH, widely used in the treatment of tuberculosis, may induce leukemia and tumors in laboratory animals. Metronidazole is also mutagenic to some strains of bacteria,[6] a response shared by many antitumor chemotherapy agents. The significance of the findings for a drug with potential benefit in patients with anaerobic infections has not been determined as yet. The risk-benefit factor has not been established.

REFERENCES

1. Gorbach, S. L., and Thadepalli, H.: Clindamycin in pure and mixed anaerobic infections, Arch. Intern. Med. **134:** 87, 1974.
2. Sutter, V. L., Vargo, V. L., Finegold, S. M., and Bricknell, K. S.: 1975 Anaerobic Bacteriology Manual, Los Angeles, 1975, University of California.
3. Ledger, W. J., and Kriewall, T. J.: The fever index: A quantitative indirect measure of hospital acquired infec-

tion in obstetrics and gynecology, AM. J. OBSTET. GYNECOL. **115:** 514, 1973.
4. Ralph, E. D., Clarke, J. T., Libke, R. D., Luthy, R. P., and Kirby, W. M. M.: Pharmokinetics of metronidazole as determined by bioassay, Antibiot. Agents Chemother. **6:** 691, 1974.
5. Rustia, M., and Shubik, P.: Induction of lung tumors and malignant lymphomas in mice by metronidazole, J. Natl. Cancer. Inst. **48:** 721, 1972.
6. Voogd, C. E., Bander Stel, J. J., and Jacobs, J. J.: Mutagenic action of nitromidazoles. I. Metronidazole, nimorazole, dimetridazole, ionidazole, Mutat. Res. **26:** 483, 1974.

Newest Methods in the Diagnosis of Cancer

A two-day multidisciplinary symposium, "Newest Methods in the Diagnosis of Cancer," will be presented October 6 and 7, 1976. This symposium will be organized by the staff at Roswell Park Memorial Institute and will be chaired by Dr. Clara Ambrus. It will be accredited by the American Medical Association. For further information, contact: Professional Education Office, Roswell Park Memorial Institute, 666 Elm St., Buffalo, New York 14263.

Colonic pseudo-obstruction following termination of pregnancy and uterine operation

IAN A. SPIRA, M.B., CH. B.(CAPE TOWN), F.R.C.S.(EDIN.), F.C.S.(SOUTH AFRICA), F.A.C.S.
WILLIAM I. WOLFF, M.D., F.A.C.S.
New York, New York

Colonic pseudo-obstruction refers to a condition in which physical and radiologic findings identical to those associated with mechanical obstruction of the large bowel are found but in which no organic cause of the colonic distention is present. Cases of this condition have been reported in the world literature, of which 40 per cent have followed the termination of pregnancy or uterine operation. Three cases of this syndrome are presented. One followed normal vaginal delivery; one followed cesarean section, and the third followed elective abdominal hysterectomy. The literature on the subject is reviewed, and a possible anatomicophysiologic explanation, based upon a sympathetic-parasympathetic neurostimulatory imbalance, is put forward.

COLONIC PSEUDO-OBSTRUCTION refers to a condition in which physical and radiologic findings identical to those associated with mechanical obstruction of the large bowel are found but in which no organic cause of the colonic distention is present. Although this condition may be associated with a variety of etiologic factors, it has been shown to be associated with the termination of pregnancy and uterine operation in about 40 per cent of cases (Table I). In the early postpartum or postoperative period, the patients develop crampy abdominal pain, increasing abdominal distention, vomiting, and constipation. On examination, the patient's abdomen is found to be distended with normal or hyperactive bowel sounds. X-ray examination reveals a distended colon. The colonic distention may be so marked that spontaneous rupture of the cecum can occur.[1-5] Despite this, further investigation of the patient reveals no mechanical cause for the obstruction.

We wish to present three cases of this syndrome: one following normal pregnancy, one following cesarean section, and one following abdominal hysterectomy. The literature on the subject will be reviewed, and we will add our thoughts as to the etiology and pathogenesis of the condition.

From the Department of Surgery, Beth Israel Medical Center and Mount Sinai School of Medicine of the City University of New York.
Received for publication June 17, 1975.
Revised November 5, 1975.
Accepted December 8, 1975.
Reprint Requests: Dr. Ian A. Spira, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, New York 10003.

Case reports

Case 1 (C. M.). This 26-year-old white woman, para 1, gravida 1, was admitted in labor and had an uneventful vaginal delivery. Postpartum, the patient was well until the third postpartum day when she began complaining of cramping abdominal pains and increasing abdominal distention. On examination, the patient had a markedly distended abdomen. There was no tenderness, guarding, or rigidity. The uterus was palpable two fingerbreadths below the umbilicus. Bowel sounds were increased. Rectal examination was normal. X-ray of the abdomen revealed marked distention of the colon down to the level of the sigmoid colon (Fig.1). Serum electrolytes were within normal limits, and the blood urea nitrogen was 8 mg. per cent. Sigmoidoscopy to a level of 25 cm. from the anal verge was unremarkable.

An emergency Gastrografin* enema was performed which demostrated a distended colon with no evidence of mechanical obstruction.

The patient was given nothing by mouth and received intravenous fluids. Over the next two days, the patient began passing flatus, and the abdominal distention subsided. The rest of the postpartum course was uneventful.

Case 2 (M. D.). A 24-year-old black woman was admitted on August 7, 1973, with a diagnosis of term

*E. R. Squibb, P. O. Box 4000, Princeton, New Jersey 08544.

Table I. Etiologic survey of cases of pseudo-obstruction of the colon obtained from the literature

Author	*No. of cases*	*Intra-abdominal inflammation*	*Retroperitoneal disease*	*Cardiac failure*	*Myocardial infarction*	*Septic abortion*	*Normal pregnancy*	*Cesarean section*	*Pelvic operation*
Bryk and Soong	46	18	6	7		2			
Cannel and Tovee	10						2	8	
Carfasquilla	3								
Caves and Crockard	4	1		1	1				
Colp	5				1	1			
Dunlop	1		1						
Dyer and associates	1								
Murphy	1								
Eckman	1								
Eliason and Erb	32	4					28		
Ludwig	10						10		
Heitzman and colleagues	1				1				
Hirsh	1						1		
McFarland	3				1				
McCune and Kashish	10	1					1		6
V. Mikulicz	24						18		
Millar	2							2	
Moore and Koman	1								
Morton and co-workers	8		1			4		2	1
Morton	4	1				1			
Ogilvie	2		2						
Robertson	1							1	
Rothwell-Jackson	3		1	1		1			
Stephens	4	1		2					
Stephens	2	1			1				
Wanebo	18		1	1					
Wojtalik	4		1			2			
Yeo	2								
Total	204	27	13	12	5	11	60	13	7
%		3.2	6.4	5.9	2.4	5.4	29.4*	6.4*	3.4*

*39.2 per cent.

pregnancy. She had had two previous cesarean sections for cephalopelvic disproportion due to a small pelvis. The previous cesarean sections were unremarkable. The patient had a past history of heroin addiction and had recurrent urinary tract infections during the current pregnancy.

On August 7, she underwent the third cesarean section. She did well initially, but on the third postoperative day it was noted that the abdomen was distended. The patient was passing flatus, and bowel sounds were present. By the following day, the abdominal distention had increased markedly, and the temperature was elevated. Bowel sounds were present, and x-ray examination of the abdomen revealed a distended colon with air fluid levels (Fig. 2).

A Cantor tube was passed on the fifth postoperative day. The abdomen remained markedly distended, despite the fact that the patient was passing flatus. The patient showed no improvement, and an emergency barium enema was performed the following day. It showed the entire colon to be markedly distended, particularly the cecum and ascending colon. There was no evidence of any mechanical obstruction in the colon. The patient's electrolytes and blood urea nitrogen levels were within normal limits throughout this period.

Shortly after the barium enema, the patient began passing large amounts of watery stool. At the same time, the abdominal distention decreased and completely disappeared shortly thereafter.

Case 3 (C. H.). This 70-year-old white woman was admitted on September 18, 1973, for elective hysterectomy with a diagnosis of endometrial adenocarcinoma. At the time of admission, she gave no history of any bowel complaints, and examination of the abdomen and rectum was normal.

A hysterectomy was performed without incident on the following day. The postoperative course was uneventful until the fifth day, when marked abdominal distention was noted. Scout films of the abdomen showed marked dilation of the cecum and ascending colon (Fig. 3). Dilated small bowel loops were also present.

Myenteric plexus lesion	*Lead poisoning*	*Trauma: pelvis and abdomen*	*Idiopathic (unknown)*	*Spinal injury*
		2	11	
		1	2	
			1	
			3	
1				
	1			
			1	
			2	
			2	
			6	
		1		
			2	
			1	
	1	2	13	
			2	1
1	2	6	46	1
0.5	1	2.9	22.5	0.5

The patient was given nothing by mouth; a Cantor tube was passed, and intravenous fluids were given. When no improvement was noted the following day, a barium enema was performed. Barium flowed freely from the rectum to the middle-ascending colon, where a stoppage was demonstrated. A markedly dilated cecum, measuring 12 to 13 cm. in diameter, was also seen. The evacuation film revealed some barium in the grossly dilated cecum.

In view of the above findings, a laparotomy was performed. The cecum was found to be enormously distended, but neither mechancial blockage nor cecal volvulus was present. A cecostomy was performed.

The bowel promptly decompressed, and the postoperative course was uneventful. A repeat barium enema performed on October 12 was normal, with no evidence of colonic obstruction.

Background

Colonic pseudo-obstruction has been described in the literature under a variety of names such as "ileus of the colon"[6] "idiopathic large bowel obstruction,"[7] and "spastic ileus."[8] The reason for the many names has been a lack of a clear understanding of the true etiology and pathogenesis of this condition.

Although colonic pseudo-obstruction was probably first described by Murphy,[9] in 1896, the first to relate the termination of pregnancy to the condition was Von Mikulicz in 1926.[10] He described 24 cases of colonic pseudo-obstruction, of which 18 followed normal pregnancy. Thereafter, through 1974, a further 80 cases were described directly related to termination of pregnancy or antecedent uterine operation. Since a search of the literature revealed a total of 204 cases of colonic pseudo-obstruction from all etiologies, the 80 cases represented 39.2 per cent of the total (Table I).

Comment

In order to determine the pathogenesis of this condition, one must understand the distribution of the sympathetic and parasympathetic nerve fibers to the colon and uterus and their physiologic effects.

The autonomic nerves are classified as sympathetic and parasympathetic. More recently, however, the terms "cholinergic" and "adrenergic" have been accepted, depending upon whether they liberate acetylcholine or catecholamines at their final synapse. Although there is considerable mixing,[11] most parasympathetic nerves are cholinergic while sympathetic nerves are adrenergic.

The parasympathetic nerve supply to the gastrointestinal smooth muscle comes mainly from the vagus, with the distal colon receiving additional extrinsic parasympathetic innervation from the sacral segments at the level of the second sacral vertebra to the level of the fourth sacral vertebra (Fig. 4).[12]

Parasympathetic fibers do not directly innervate the smooth muscle cells but synapse with nerve cells in the enteric plexus. Therefore, their function is to increase or decrease the excitability of the reflex centers and not to initiate muscular activity directly.[11]

The sympathetic supply to the cecum, appendix, and ascending and proximal transverse colon is by way of nerves which arise from the superior mesenteric plexus (Fig. 4). This plexus is a derivative of the aortic plexus through which it also receives fibers from the celiac plexus. The distal large bowel is supplied by sympathetic fibers which arise from the upper and lower divisions of the hypogastric plexus. The preganglionic fibers end in the celiac, superior or inferior mesenteric, or aortic ganglia. Most of these postganglionic fibers that reach the bowel are concerned with the vasomotor supply of the numerous blood vessels in the intestine, but some go to the smooth muscles.[11]

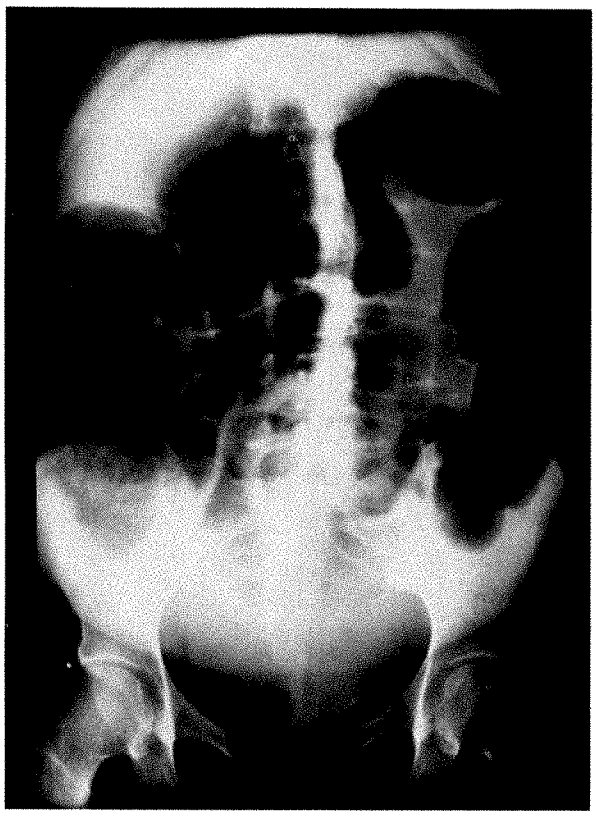


Fig. 1. Roentgenogram of the abdomen revealing a markedly distended colon.

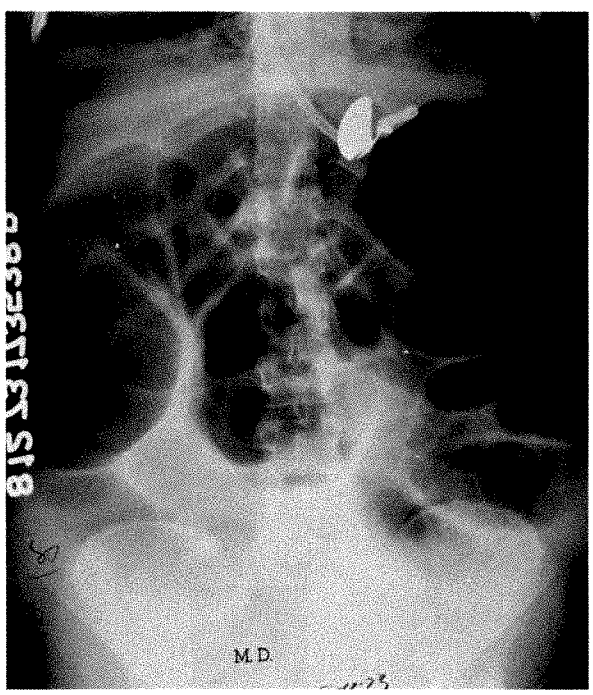


Fig. 2. Roentgenogram of the abdomen revealing a markedly distended colon.

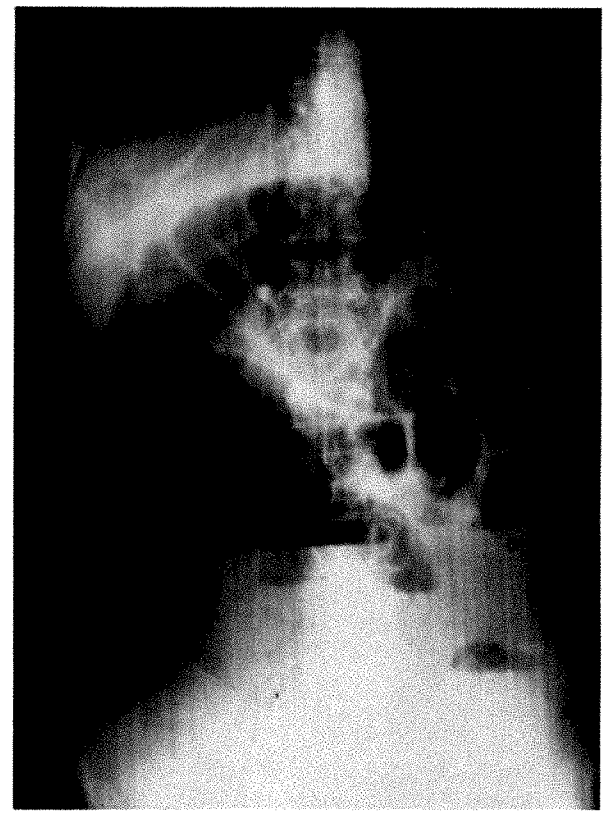


Fig. 3. Roentgenogram of the abdomen revealing marked dilatation of the cecum and ascending colon.

In the large intestine, stimulation of the parasympathetic nerves mainly causes increased activity. Stimulation of the sympathetic nerves gives rise to a very confusing picture. Some investigators report inhibitory effects, and others report only motor effects, whereas still others report inhibition of the walls of the viscera with contraction of the sphincters. This latter view is the most widely held.[11]

Afferent and efferent nerves from the uterus pass along pathways identical to those of the distal colon (Fig. 4). As a result of this anatomic relationship, we will postulate how pregnancy, cesarean section, and other uterine operations, by interfering with the normal parasympathetic outflow from segments at the level of the second, third, and fourth sacral vertebrae can disrupt the neurostimulatory balance between the proximal (vagus supplied) and distal colon and between parasympathetic and sympathetic nerve supplies to the distal colon, causing a functional obstruction at the level where proximal and distal nerve supplies overlap.

The postulate is that, as a result of labor, cesarean section, or uterine operation, there is an avalanche of afferent stimuli passing from the uterus through the pelvic plexus to the segments at the levels of the

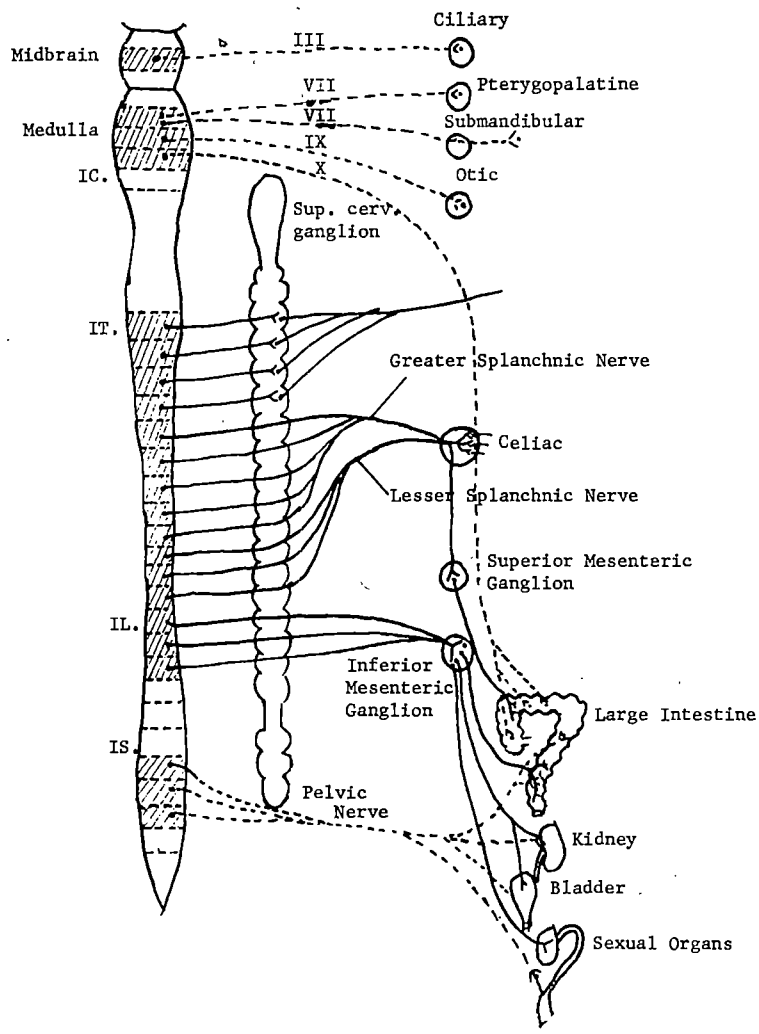


Fig. 4. Sympathetic and parasympathetic nerve supply to the colon and uterus.

second, third, and fourth sacral vertebrae. This could result in a block to the efferent parasympathetic supply which also arises at the levels of the second, third, and fourth sacral vertebrae. Thus, we are left with a situation in which the proximal colon, with its nerve supply intact, has normal tonus and normal peristalsis and mass movements, while the distal colon is in an inert state as a result of having its stimulating parasympathetic supply removed while the inhibitory sympathetic supply remains intact. In effect, a functional obstruction could exist at the point at which proximal and distal nerve supplies overlap. Since the obstruction would, in the true sense, be functional, it can be appreciated how in cases where the condition persists the distention may become so marked as to result in cecal perforation, splitting of the teniae coli, or even gangrene of the proximal colon.

It remains unclear as to why this condition should arise in only a small percentage of terminations of pregnancy or operations on the uterus. It may be that in these cases complications arise that result in the blockading avalanche of afferent stimuli. There is no note in the literature as to whether the labors of patients developing colonic pseudo-obstruction were normal or complicated or whether the cesarean sections were elective or emergency. It will be interesting to note in future cases whether a parasympathetic drug such as Urecholine* will be benefical.

Diagnosis and management

The importance of this condition lies in its detection. Early diagnosis may avoid unnecessary surgical intervention. At the same time, appreciating the possible complications of the syndrome, the physician will be

*Merck Sharp & Dohme, Div. Merck & Co., Inc., West Point, Pennsylvania 19486.

alerted to watch for danger signals and to institute appropriate measures, including operation, at the proper time.

The first important aid in diagnosis is the type of patient. First, we have the large group of patients who are postpartum or who had cesarean section.[10, 13, 14] These are usually younger women in whom carcinoma of the colon is uncommon. In this group, the development of a large distended colon should alert the surgeon to the possibility of pseudo-obstruction.

Early emergency water-soluble contrast Gastrografin enema should be instituted. This will confirm or exclude a mechanical obstruction to the colon. Furthermore, in some cases of pseudo-obstruction, the Gastrografin will exert a therapeutic effect, and resolution of the distention will follow the enema. However, the absence of a mechanical obstruction does not relieve the surgeon of his responsibility to closely observe the patient. It is well documented that pseudo-obstruction of the colon may lead to perforation of the cecum,[1-5] splitting of the teniae coli,[15] or, in some cases, gangrene of the cecum and ascending colon. Close monitoring of the patient's vital signs and regular examination of the abdomen are essential. The patient's electrolytes should be checked regularly, and any abnormality should be corrected. Finally, frequent radiologic evaluation of the abdomen to assess the degree of colonic distention must be performed.

Although the point at which cecal distention culminates in perforation depends upon a number of factors, including the rapidity of the dilatation, systemic circulatory support, oxygenation of the tissue, etc., the work of Lowman and Davis[16] suggests that when the diameter of the cecum, viewed radiologically exceeds 10 cm., danger of cecal perforation exists. This becomes an important measurement, and at this stage careful evaluation of the abdominal signs at frequent intervals becomes mandatory. Any deterioration in the patient's clinical condition should initiate immediate surgical intervention. In most cases, all that is required is a tube cecostomy. This decompresses the colon, prevents perforation, and allows an uneventful recovery. In some cases where there is extensive splitting of the teniae coli or gangrene of the cecal wall, a colonic resection may be required. However, if surgical intervention has been timely, this is rarely necessary.

Whether the patient recovers spontaneously or requires proximal decompression, it is absolutely essential to investigate her fully prior to discharge. Barium enema and colonoscopy should be performed. Fortunately, for most patients, an episode of pseudo-obstruction of the colon represents a once-in-a-lifetime incident. However, it can recur in some patients. If it occurs in a woman postpartum or following cesarean section, one must be on the alert in subsequent pregnancies.

REFERENCES

1. Albers, J. H., Smith, L. and Carter, R.: Perforation of the cecum, Ann. Surg. **143:** 251, 1953.
2. Carasquilla, C., Arbulaa, A., Fromm, S., and Lucas, C.: Cecal perforation due to adynamic ileus, Dis. Colon Rectum **13:** 252, 1970.
3. Eckman, W. G., Wenzke, F., and Asramson, W.: Perforation of the cecum complicating adynamic ileus, Am. J. Surg. **96:** 718, 1958.
4. Hirsch, M. I. : Spontaneous rupture of the cecum. Report of a case, Cent. Afr. J. Med. **7:** 49, 1961.
5. Millar, D. R., and Orliseau, B.: Two cases of spontaneous perforation of the cecum following caesarian section, Acta Obstet. Gynecol. Scand. **45:** 254, 1966.
6. Morton, J. H., Schwartz, S. I., and Gramiak, R.: Ileus of the colon, Arch. Surg. **81:** 425, 1960.
7. Rothwell-Jackson, R. L.: Idiopathic large bowel obstruction, Br. J. Surg. **50:** 797, 1963.
8. Zimmerman, L. M.: Spastic ileus, Surg. Gynecol. Obstet. **50:** 721, 1930.
9. Murphy, J. G.: Ileus, J. A. M. A., **26:** 72, 1896.
10. Robertson, J. A., Eddy, W. A., and Vosseler, A. J.: Spontaneous perforation of the cecum without mechanical obstruction. Review of literature and case report, Am. J. Surg. **96:** 448, 1958.
11. Wojalik, R. S., Lindenauer, S. M., and Kahn, S. S.: Perforation of the colon associated with adynamic ileus, Am. J. Surg. **125:** 601, 1973.
12. Yeo, R.: Spontaneous perforation of the cecum: Case reports and a review of the literature, Postgrad. Med. **43:** 65, 1967.
13. Cannell, D. E., and Tovee, E. B.: Post-partum obstruction of large bowel, Postgrad. Med. **21:** 231, 1957.
14. Eliason, E., and Erb, W. H.. Intestinal obstruction complicating pregnancy, Surgery **1:** 686, 1969.
15. Norton, L., Young, D., and Scribner, R.: Management of pseudo-obstruction of the colon, Surg. Gynecol. Obstet. **138:** 595, 1974.
16. Lowman, R. M., and Davis, L.: An evaluation of cecal size in impending perforation of the cecum, Surg. Gynecol. Obstet. **103:** 711, 1956.

Primary prostaglandins in amniotic fluid in pregnancy and spontaneous labor

F. DRAY

R. FRYDMAN

Paris and Clamart, France

Primary prostaglandins have been measured by radioimmunoassay in the amniotic fluid of 80 patients. In late pregnancy, PGE_2 was higher than $PGF_{2\alpha}$ with an increase around 36 weeks (378 ± 71 pg. per milliliter) without significant modification until term. $PGF_{2\alpha}$ increased too, but only significantly at term. During spontaneous labor, PGE_2 and $PGF_{2\alpha}$ were higher than before the onset of labor. Through serial determinations in five patients, two steps can be distinguished: the first one with stable levels but large oscillations of PGE_2 and $PGF_{2\alpha}$ and the second one starting at a variable stage of cervical dilatation with inversion of $PGE_2/PGF_{2\alpha}$ ratio (<1) and followed by an increase of both compounds more pronounced for $PGF_{2\alpha}$. It appears that PGE_2 is concerned with the initiation of parturition while both PG's and mainly $PGF_{2\alpha}$ are in relation to the contractions and the duration of labor.

RADIOIMMUNOLOGIC and gas-chromatographic mass-spectrometric techniques have been recently used for the measurement of F prostaglandins (PGF_α)[1–4] or E prostaglandins (PGE)[5] in human amniotic fluid. PGF_α identified as $PGF_{2\alpha}$[3] was high prior to the onset of labor as compared to midpregnancy; levels stayed high during labor and were proportional to the degree of cervical dilatation. PGE_2 was detected only during labor and a proportional increase was also observed with cervical dilatation.[3] These recent results are inconsistent with those previously published by Karim and Devlin,[6] who reported identical concentrations of PGE's, mainly PGE_1, in late pregnancy and in labor.

Recently we have reported a specific and sensitive radioimmunoassay[7–10] that allows us to measure simultaneously PGE_1, PGE_2, and PGF_α (1 + 2) in the same sample. We have applied this technique to the measurement of primary prostaglandin levels in amniotic fluid during pregnancy and spontaneous labor. In this paper we report our results and discuss the respective roles of PGE_2 and $PGF_{2\alpha}$.

Service de Gynécologie et d'Obstétrique, Hôpital Antoine Béclère and Unité de Radioimmunologie Analytique.

This work was supported in part by grants INSERM No. 74 07 802, No. 23 75 46, and by CNAMTS 1975.

Received for publication July 14, 1975.

Revised December 29, 1975.

Accepted December 31, 1975.

Reprint requests: Dr. F. Dray, Unité de Radioimmunologie Analytique, Institut Pasteur 28, rue du Dr. Roux 75724–Paris Cedex 15, France.

Materials and methods

From 80 patients in the Department of Obstetrics and Gynecology, Antoine Béclère Hospital, Clamart, 160 specimens of amniotic fluid were obtained. Forty-three patients were 90 to 295 days from the last menstrual period and 37 patients were in labor.

Amniotic fluid was collected by abdominal amniocentesis in early pregnancy (19 patients) and in late pregnancy until term and before labor (24 patients). The fluid was obtained by artificial rupture of the membranes during uncomplicated spontaneous labor after placental location by the echographic method. In five patients serial samples were collected during labor from a sterile polythene catheter (diameter 16 mm. length 60 cm.) maintained in the amniotic cavity until expulsion of the fetus. In all cases, samples were collected into sterile tubes and centrifuged immediately at 2,000 g at 5° C. for 20 minutes; the supernatant was decanted and kept at −20° C. for 2 to 7 days until assay. Samples obviously contaminated with blood or meconium were discarded. In four cases abdominal amniocentesis was performed twice within an interval of 1 to 3 weeks, between 33 and 39 weeks of gestation. Except for three cases with anencephalic fetuses, only patients with uncomplicated pregnancies were included in the present study.

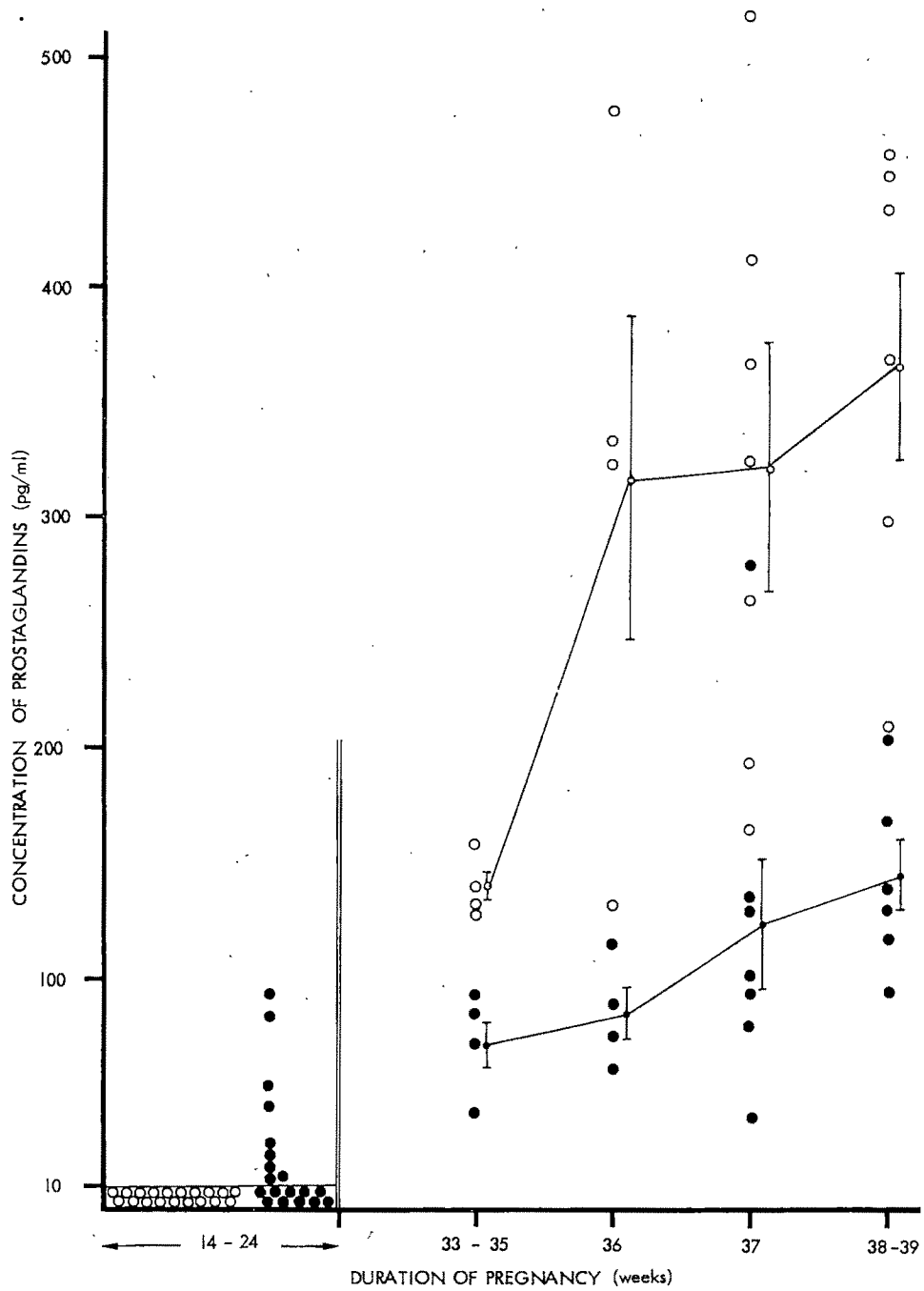


Fig. 1. Amniotic fluid levels of PGE_2 (o——o) and $PGF_{2\alpha}$ (•——•) from the early stage of pregnancy (14 to 24 weeks), until term and before labor. In late pregnancy, mean and standard error (M ± S.E.) were calculated after distribution of the 21 individual values in four groups.

Primary prostaglandins in amniotic fluid (0.5 to 5 ml.) were determined as previously described.[9] Briefly, samples were acidified at pH 3 with citric acid and PG's extracted with a mixture of ethyl acetate/cyclohexane (v/v, 1 : 1) and purified in a silicic acid column. The eluted fractions containing PGE and PGF_α, respectively, were dried and dissolved in the buffer used for all solutions: 0.1M phosphate, pH 7.4, with 0.9 per cent NaCl, 0.1 per cent sodium acid, and 0.1 per cent gelatine. The amount of buffer added was chosen according to the sensitivity of each radioimmunologic system. The recovery of radioactive prostaglandins

Table I. Binding parameters of the prostaglandin antisera (AS) selected for this study

Antisera (AS)	*Ka (average)*	*Cross reactions (%)*				
		$F_{1\alpha}$	$F_{2\alpha}$	E_2	E_2	*A/B*
$PGF_{2\alpha}$-AS	$6 \times 10^9\ M^{-1}$	100	100	<1	<1	<1
PGE_1-AS	$1.9 \times 10^{10}\ M^{-1}$	<1	<1	100	3	<1
PGE_2-AS	$1.8 \times 10^{10}\ M^{-1}$	<1	<1	2.7	100	<1

Table II. PGE_2, $PGF_{2\alpha}$, and $PGE_2/PGF_{2\alpha}$ ratio in amniotic fluid in late pregnancy: mean values (pg./ml.), standard error (S.E.), and significance of the differences between the four groups distributed in relation to the stage of gestation.

	PGE_2		*$PGF_{2\alpha}$*		*$PGE_2/PGF_{2\alpha}$*	
	Mean	*S.E.*	*Mean*	*S.E.*	*Mean*	*S.E.*
Group I, 33-35 weeks (n = 4)	140	6.4	72.2	11	2.09	0.36
Group II, 36 weeks (n = 4)	318	71	85	12.1	3.68	0.72
Group III, 37 weeks (n = 7)	322	47.4	123.3	28.9	3.32	0.77
Group IV, 38-39 weeks (n = 6)	370	40.5	142.7	16.4	2.73	0.39
II/I	$p < 0.05$		NS*		$p < 0.1$	
III/I	$p < 0.01$		NS		NS	
IV/I	$p < 0.001$		$p < 0.01$		NS	
III/II	NS		NS		NS	
IV/III	NS		NS		NS	

*NS = nonsignificant.

added before extraction was tested on an aliquot of this solution. Samples where the final recovery was inferior to 75 per cent were discarded; all assays were performed in duplicate and at two dilutions. Tritiated PG's were used as tracers (specific activities in Ci/mM: $PGF_{1\alpha}$, 79; PGE_1, 87; PGE_2, 125). Rabbit antibodies against $PGF_{2\alpha}$ and PGE_2 and sheep antibodies against PGE_1 were raised after immunization with the corresponding PG conjugated to bovine serum albumin. Association constants (Ka average) and cross reactions of antisera selected for this study are shown in Table I. The mixture (diluted antiserum, 0.1 ml.–standard or extract, 0.1 ml.–tracer, 8,000 d.p.m., 0.1 ml.) was incubated for 2 hours at 4° C. One milliliter of ice-cold dextran-coated charcoal was then added. Ten minutes later the tubes were centrifuged at 4° C. for 5 minutes at 2,000 g. The supernatant fluid was decanted into plastic vials and 10 ml. of Instagel (Packard) were added. Counting was performed in an "Intertechnique Scintillator Spectrometer" with an efficiency of 27 per cent. The comparative sensitivities of the antiprostaglandin antibodies can be indicated by the amount of PG standard which is necessary to produce 15 per cent displacement of bound radioactivity (i.e., 15 per cent change in the bound : free ratios on the standard curve) in the radioimmunoassay; these values for $PGF_{2\alpha}$, PGE_1, and PGE_2 were 7.5, 5, and 2 pg., respectively.

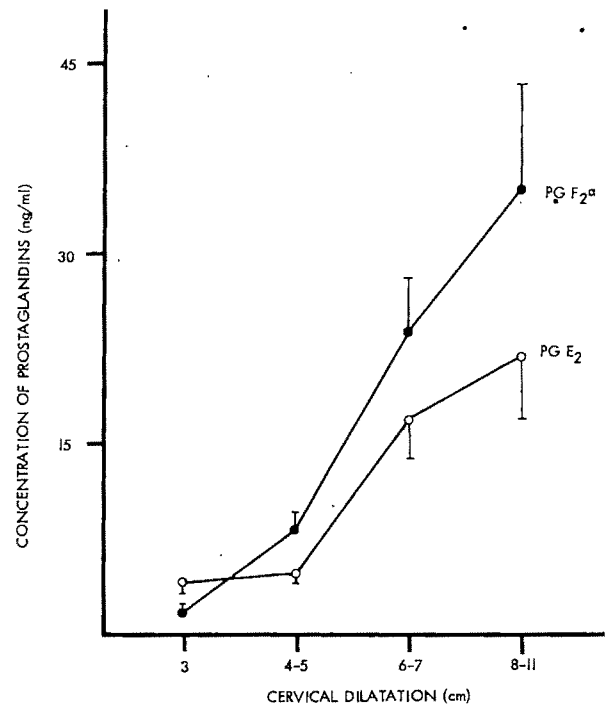


Fig. 2. Amniotic fluid levels of PGE_2 (o——o) and $PGF_{2\alpha}$ (•——•) during spontaneous labor. Mean and standard error (M ± S.E.) were calculated after distribution of the 37 individual values in four groups.

Results

Early pregnancy. Nineteen samples of amniotic fluid were collected by amniocentesis between 14 and 24 weeks of pregnancy. PGE_1 and PGE_2 were constantly undetectable (<10 pg.), whereas the $PGF_{2\alpha}$ level was between 10 and 94 pg. in nine cases and under 10 pg. in the 10 others (Fig. 1). There was no correlation between $PGF_{2\alpha}$ values and the stage of pregnancy. No uterine activity was detected by external tocography at the time of sampling.

Late pregnancy before the onset of labor. Results from 21 specimens of amniotic fluid obtained between 33 and 39 weeks were distributed in four groups in relation with the stage of pregnancy. The individual values are shown in Fig. 1 and the statistical data are reported in Table II. PGE_1 was undetectable or below one tenth of the PGE_2 values. PGE_2 was detectable at 33 to 35 weeks (Group I), increased significantly

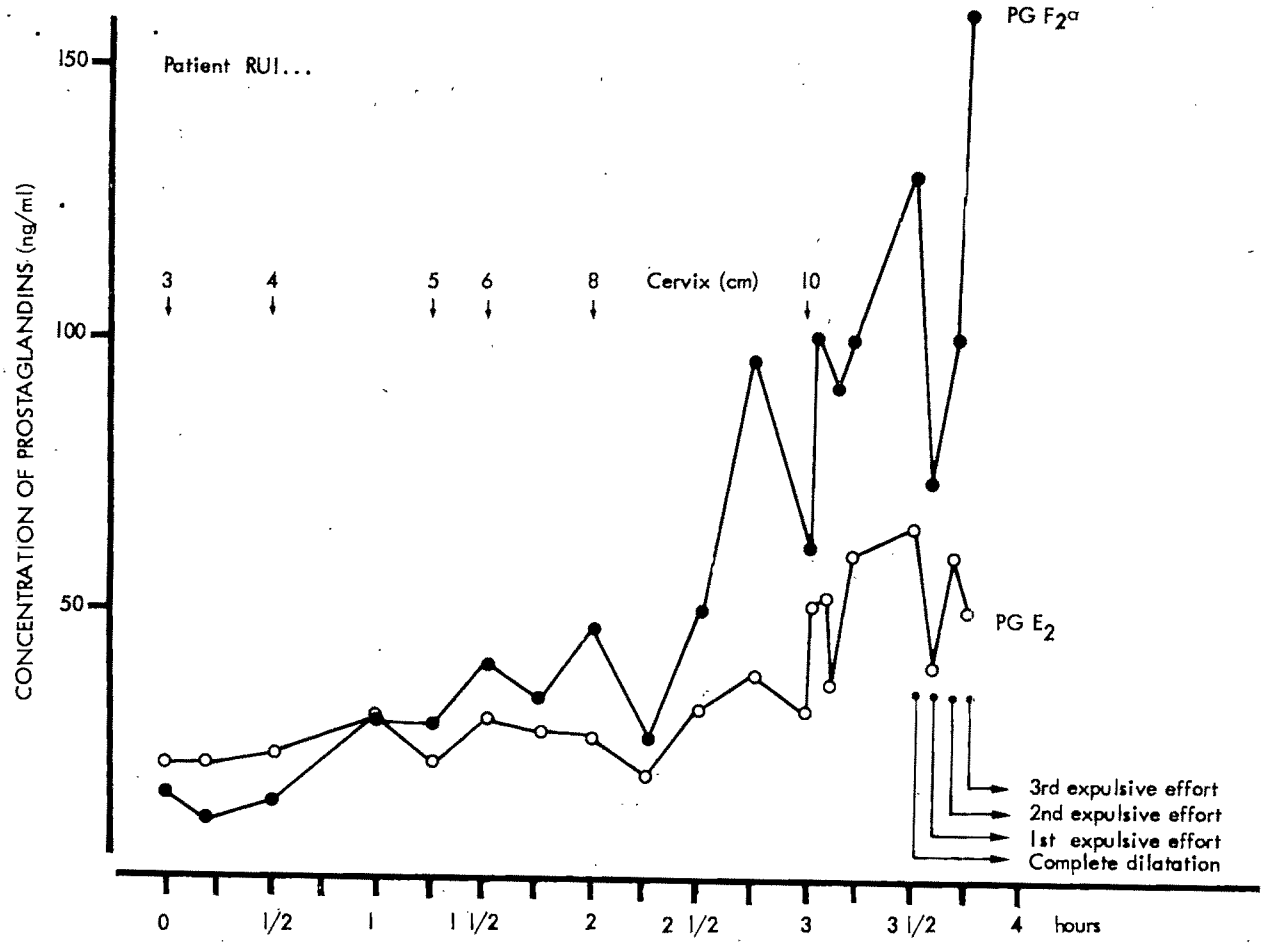


Fig. 3*A*. Amniotic fluid levels of PGE_2 (o——o) and $PGF_{2\alpha}$ (•——•) in Patient R. U. I. Multiple samples were collected through the catheter at the artificial rupture of membranes and during a variable period of spontaneous labor.

($p < 0.05$) at 36 weeks (Group II), and did not change further until term. We detected that $PGF_{2\alpha}$ values were very close in the first three groups and a significant increase appeared only in Group IV. The $PGE_2/PGF_{2\alpha}$ ratio was always superior to 1, with a significant difference between Groups I and II.

PGE_2 and $PGF_{2\alpha}$ values in eight samples obtained by two repeated amniocenteses from four patients are shown in Table III. In each case PGE_2 was higher in the second sample and PGE_2 was unchanged.

In amniotic fluid from three late pregnancies with anencephaly (Table IV) PGE_2 was low; $PGF_{2\alpha}$ was low in one case and normal in the two others; the $PGE_2/PGF_{2\alpha}$ ratio was below 1 in two cases and equal to 1 in one case.

During labor. Results from 37 samples of amniotic fluid collected during labor after artificial rupture of the membranes were distributed in four groups in relation with the cervical dilatation (Fig. 2 and Table V). At the very early stage of dilatation (Group I), PGE_2 and $PGF_{2\alpha}$ were already high and their respective mean was 10-fold higher than just before the onset of labor. Their values increased throughout the labor mainly for $PGF_{2\alpha}$ so that the $PGE_2/PGF_{2\alpha}$ ratio became inferior to 1 in Groups II, III, and IV. PGE_1 was always undetectable or below one tenth of the PGE_2 values.

In another study, serial samples of amniotic fluid were collected in five patients during spontaneous labor. First samples were obtained immediately after artificial rupture of the membranes. Figs. 3 and 4 represent individual PGE_2 and $PGF_{2\alpha}$ in relation to the progress of cervical dilatation. In Fig. 3*A* (Patient R. U. I.), 20 samples were collected during 4 hours between 3 cm. dilatation and expulsion. From 3 to 8 cm., PGE_2 was unchanged and $PGF_{2\alpha}$ increased weakly and became superior to PGE_2. Then PGE_2 and mainly $PGF_{2\alpha}$ increased until expulsion. In Fig. 3*B* (Patient B. O. D.), six samples were collected in 2½ hours between 3 and 8

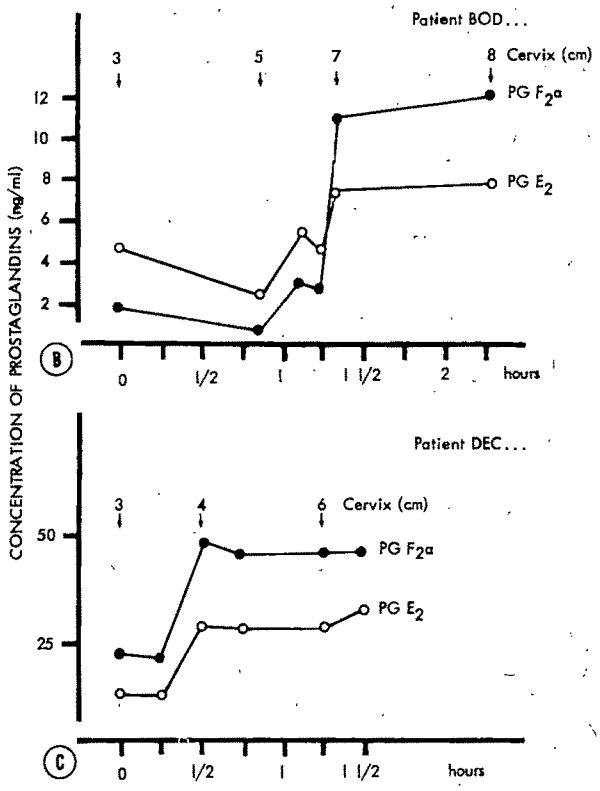


Fig. 3*B*. Patient B. O. D.; see legend, Fig. 3*A*.

Fig. 3*C*. Patient D. E. C.; see legend, Fig. 3*A*.

cm. PG's were unchanged until 7 cm.; then they increased with an inversion of the $PGE_2/PGF_{2\alpha}$ ratio. In Fig. 3*C* (Patient D. E. C.), six samples were collected during 1½ hours between 3 and 6 cm. $PCF_{2\alpha}$ was superior to PGE_2 in the six samples and remained so throughout the collection period. In Fig. 3*D* (Patient J. A. C.), 11 samples were collected during 1½ hours between 5 and 11 cm. Until 8 cm. there was no significant modification in the values of each PG. Then $PGF_{2\alpha}$ became superior to PGE_2 and increased more than PGE_2 until 11 cm. In Fig. 4 (Patient G. U. E.), nine samples were collected during 30 minutes from 2 to 3 cm. and 32 samples were continuously withdrawn during 15 minutes from 3 to 5 cm. PGE_2 was always superior to $PGF_{2\alpha}$. Large, frequent, and roughly parallel oscillations were observed in PGE_2 and $PGF_{2\alpha}$ levels, without relation to uterine contractions.

Comment

Selected antisera to prostaglandins and tritiated tracers with high specific activities allowed us to develop specific and sensitive radioimmunoassays. Extraction and chromatography were used on all samples throughout this work. However, comparative assays

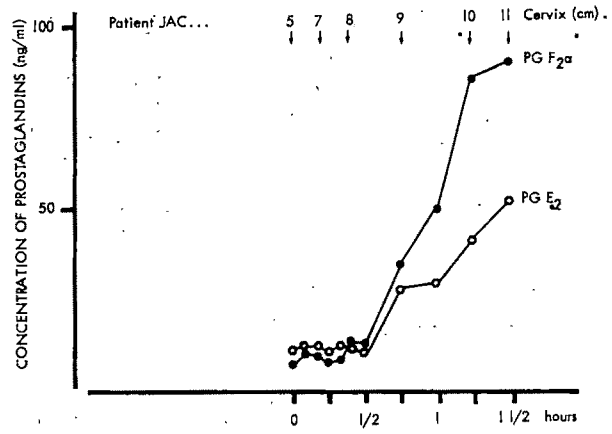


Fig. 3*D*. Patient J. A. C.; see legend, Fig. 3*A*.

Table III. Prostaglandins PGE_2 and $PGF_{2\alpha}$ in amniotic fluid at two different periods of gestation and before the onset of labor (pg./ml.)

Weeks	*Patients' names*	*Delay from the onset of labor (days)*	PGE_2	$PGF_{2\alpha}$
30	Qui	24	60	80
33		2	130	71
35	Pet	20	140	95
37		4	368	93
35	Dub	30	131	42
37		14	265	39
37	Cam	7	165	130
38		1	450	131
33	Ais	60	63	95
37		30	76	111

subsequent to this study showed that the chromatographic step could be omitted when testing samples collected during labor. The high dilution of amniotic fluid required by the high levels of PG's in that period suppressed the interference of nonspecific factors which appeared with undiluted amniotic fluid. On the other hand, rigorous conditions for collecting and handling amniotic fluid samples were observed; samples not perfectly clear or scarcely contaminated with blood or meconium were discarded. These precautions insured us that our PG values were not influenced by in vitro production or by release from cellular elements.

We are reporting in this paper the first study on primary prostaglandins in amniotic fluid from the same patient and their evolution from early pregnancy to the end of spontaneous labor.

At first we confirmed the results of other authors[1, 2, 4–6] about $PGF_{2\alpha}$: we found less $PGF_{2\alpha}$ at midpregnancy than at term prior to labor; then the $PGF_{2\alpha}$ values were

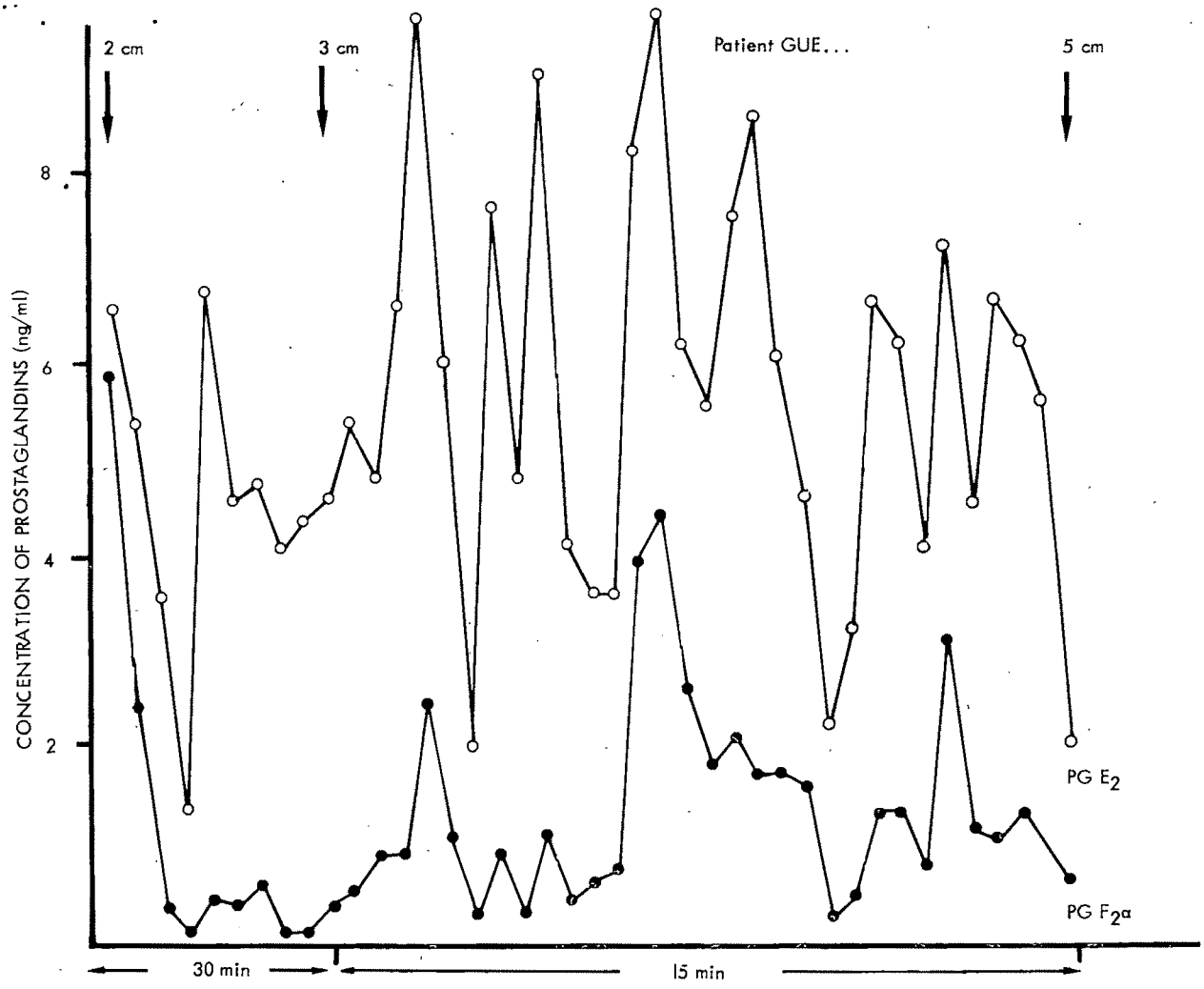


Fig. 4. Amniotic fluid levels of PGE_2 (o——o) and $PGF_{2\alpha}$ (•——•) in Patient G. U. E. after multiple samples and continuous withdrawal.

Table IV. Prostaglandins PGE_2 and $PGF_{2\alpha}$ in amniotic fluid of three patients with anencephalic fetus and before labor

Weeks	*Patients' names*	*PGE_2*	*$PGF_{2\alpha}$*	*$E_2/F_{2\alpha}$*
35	Lan	58	92	0.63
38	Gan	128	125	1.06
39	Cou	55	76	0.72

higher during labor and increased further at the end of it.

Moreover, the specificity of our PGE_1 antiserum permitted us to demonstrate that PGE_1 is either absent or a minor component in amniotic fluid of normal pregnancy until term and during spontaneous labor. Those results are opposite to those of Karim and Devlin[6] and Singh and Zuspan,[11] who detected PGE_1 by nonspecific methods. Keirse, Flint, and Turnbull[3] showed that $PGF_{1\alpha}$ measured by mass spectrometry is also a minor component of amniotic fluid as compared to $PGF_{2\alpha}$. These results and ours establish firmly that essentially PGE_2 and $PGF_{2\alpha}$ are present in amniotic fluid during normal pregnancy.

Before labor, our results showed striking variations of relative values of PGE_2 and $PGF_{2\alpha}$: at 33 weeks PGE_2 was high as compared to $PGF_{2\alpha}$. At 36 weeks PGE_2 increased further and remained high until term. Increase in $PGF_{2\alpha}$ occurred close to term. These results are opposite to those of Keirse and Turnbull,[5] who could not detect PGE_2 by gas-liquid chromatography in 10 out of 12 samples taken before the onset of labor. They are also at variance with those of Hibbard and associates,[2] who observed a progressive increase of $PGF_{2\alpha}$ from the thirty-seventh week until term. The

Table V. PGE_2, $PGF_{2\alpha}$, and $PGE_2/PGF_{2\alpha}$ ratio in amniotic fluid during spontaneous labor: mean values (pg./ml.), standard error (S.E.), and significance of the differences between the four groups distributed in relation to the cervical dilatation

	PGE_2		$PGF_{2\alpha}$		$PGE_2/PGF_{2\alpha}$	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Group I, 1-3 cm. (n = 11)	3,760	777	1,540	485	3.90	0.62
	NS		$p < 0.001$		$p < 0.001$	
Group II, 4-5 cm. (n = 13)	4,405	452	8,235	1,227	0.71	0.17
	$p < 0.001$		$p < 0.01$		NS*	
Group III, 6-7 cm. (n = 8)	17,605	3,222	24,360	4,629	0.76	0.07
	NS		NS		NS	
Group IV, 8-11 cm. (n = 5)	22,560	5,255	35,790	7,934	0.63	0.07

*NS = nonsignificant.

increase of PGE_2 that we report in this paper takes place among other events occurring around this critical period of gestation: viz., increase of myometrial contractions[12] and increase of estrogen and fall of progesterone in human plasma.[13] More studies of this period may provide evidence for interrelations between these different events.

During labor, our results point out an intricate situation. This appears first from the statistical study of the means of Table V: PGE_2 and $PGF_{2\alpha}$ did not progress in the same time and with the same amplitude and their increase was not closely related to the cervical dilatation. The results obtained in the cases where multiple samples were collected during labor are more striking, as can be seen in Fig. 3 and 4. The events seem to take place in two steps: during the first step levels of PGE_2 and $PGF_{2\alpha}$ are roughly stable with large oscillations. Fig. 4 is particularly demonstrative. The second step is characterized by an inversion of the $PGE_2/PGF_{2\alpha}$ ratio and a sudden increase of both compounds, which is more pronounced for $PGF_{2\alpha}$. Usually the inversion of the ratio takes place with a variable lag period before the increase of PGE_2 and $PGF_{2\alpha}$; these two events do not correlate closely with the stage of cervical dilatation.

It appears from this work that PGE_2 is particularly related to the preparation of parturition while both PG's, mainly $PGF_{2\alpha}$, are related to the contractions and the duration of the labor. Yet it is possible that local, contingent factors (mechanical, hemodynamic, etc.) during labor might modify the process of biosynthesis and/or inactivation of PGE_2 and/or $PGF_{2\alpha}$ and so interfere with the level and the ratio of primary prostaglandins in amniotic fluid.

We wish to thank Mrs. Soubrier for her technical assistance and Mrs. Dauphin for collecting the amniotic fluid samples.

REFERENCES

1. Salmon, J. A., and Amy, J. J.: Levels of prostaglandin $F_{2\alpha}$ in amniotic fluid during pregnancy and labour, Prostaglandins **4:** 525, 1973.
2. Hibbard, B. M., Sharma, S. C., Fitzpatrick, R. J., and Hamlett, J. D.: Prostaglandin $F_{2\alpha}$ concentrations in amniotic fluid in late pregnancy, J. Obstet. Gynecol. Br. Commonw. **81:** 35, 1974.
3. Keirse, M. J. N. C., Flint, A. P. F., and Turnbull, A. C.: F prostaglandins in amniotic fluid during pregnancy and labour, J. Obstet. Gynecol. Br. Commonw. **81:** 131, 1974.
4. Hillier, K., Calder, A. A., and Embrey, M. P.: Concentrations of prostaglandin $F_{2\alpha}$ in amniotic fluid and plasma in spontaneous and induced labours, J. Obstet. Gynecol. Br. Commonw. **81:** 257, 1974.
5. Keirse, M. J. N. C., and Turnbull, A. C.: E prostaglandins in amniotic fluid during late pregnancy and labour, J. Obstet. Gynecol. Br. Commonw. **80:** 970, 1973.
6. Karim, S. M. M., and Devlin, J. Prostaglandin content of amniotic fluid during pregnancy and labour, J. Obstet. Gynecol. Br. Commonw. **74:** 230, 1967.
7. Charbonnel, B., Soubrier, A., and Dray, F.: Dosage radioimmunologique des PGF, Société d'Endocrinologie, Ann. Endocrinol. **34:** 722, 1973.
8. Dray, F., and Charbonnel, B.: Dosage radioimmunologique des prostaglandines F_α et E_1 dans le plasma périphérique de l'homme normal, Les Prostaglandines, Octobre, 1973, Colloque de l'INSERM, p. 123.
9. Dray, F., Charbonnel, B., and Maclouf, J.: Radioimmunoassay of prostaglandins F_α, E_1 and E_2, Eur. J. Clin. Invest. **5:** 311, 1975.
10. Maclouf, J., Andrieu, J. M., and Dray, F.: Validity of PGE_1 radioimmunoassay by using PGE_1 antisera with differential binding parameters, FEBS Letters 56, 2, 273, 1975.
11. Singh, E. J., and Zuspan, F. P.: Content of amniotic fluid prostaglandins in normal, diabetic, and drug-abuse human pregnancy, Am. J. Obstet. Gynecol. **118:** 358, 1974.
12. Theobald, G. W., Robards, M. F., and Sutter, P. E. N.: Changes in myometrial sensitivity to oxytocin in woman during the last six weeks of pregnancy, J. Obstet. Gynecol. Br. Commonw. **76:** 385, 1969.
13. Turnbull, A. C., Flint, A. P. F., Jeremy, J. Y., Patten, P. T., Keirse M. J. N. C., and Anderson, A. B. M.: Significant fall in progesterone and rise in oestradiol levels in human peripheral plasma before onset of labour, Lancet **26:** 7848, 1974.

Asymptomatic bacteriuria in pregnancy: Antibody-coated bacteria, renal function, and intrauterine growth retardation

ROBERT E. HARRIS, M.D., PH.D.
VIRGINIA L. THOMAS, PH.D.
ALEXIS SHELOKOV, M.D.
Lackland Air Force Base and San Antonio, Texas

Asymptomatic bacteriuria (>100,000 microorganisms per milliliter) was found in 70 of 1,400 pregnant women without symptoms referable to the urinary tract (five per cent). With the fluorescent antibody (FA) tests, antibody-coated bacteria were demonstrated in specimens from 35 patients (50 per cent), indicating silent renal bacteriuria. Although confirmation by direct localization methods was not feasible in this group of patients, indirect evidence of renal function impairment associated with the presence of antibody-coated bacteria was suggested by results of the serum creatinine and creatinine clearance tests. The outcome of the pregnancy was compared for patients with bacteriuria (FA-negative or FA-positive tests). An association between the presence of asymptomatic renal bacteriuria and intrauterine growth retardation was noted. Thus, the patient with asymptomatic bacteriuria and a positive FA test is at greater risk of delivering an intrauterine growth-retarded infant.

RESULTS OBTAINED by using the fluorescent antibody (FA) test on urine samples from patients with chronic urinary tract infections indicate a remarkable correlation between the presence of antibody-coated bacteria in the urine and the site of infection in the kidney rather than the bladder.[1, 2] Recently, we reported the usefulness of this simple, reliable, and noninvasive FA test in obstetric patients with acute pyelonephritis; antibody-coated bacteria were usually found in urine from patients with acute pyelonephritis but not in urine from patients with cystitis.[3]

The earlier studies were made with specimens from patients who had overt urinary tract disease.[1-3] The present study was designed to investigate the origin of the bacteria in asymptomatic obstetric patients with significant bacteriuria. We were also interested in relating the results of FA tests to the patient's renal function studies, recurrence of bacteriuria after therapy, and outcome of the pregnancy.

From the Department of Obstetrics and Gynecology, Wilford Hall United States Air Force Medical Center, and the Department of Microbiology, The University of Texas Health Center at San Antonio.

The opinions expressed in this manuscript are those of the authors and not necessarily those of the United States Air Force or the Department of Defense.

Received for publication August 21, 1975.

Accepted December 3, 1975.

Reprint requests: Dr. Robert E. Harris, 6402 Red Jacket Dr., San Antonio, Texas 78238.

Patients and methods

Fourteen hundred pregnant women without symptoms referable to the urinary tract were screened for urinary tract infection at their first visit to the Wilford Hall United States Air Force Medical Center Obstetrical Clinic. Clean, voided, midstream urine specimens were cultured quantitatively by the calibrated loop technique,[4] and bacterial isolates were identified by standard biochemical methods. In cases of significant bacteriuria (≥100,000 per milliliter), the patient was contacted, and the urine was recultured at least once and often twice. All patients with confirmed asymptomatic bacteriuria were treated with antibiotics in accordance with the results of sensitivity tests.

Prior to treatment, urine specimens from these patients were tested for the presence of antibody-coated bacteria by direct immunofluorescence with the

Table I. Renal function tests in obstetric patients with asymptomatic bacteriuria

Renal function test	*Patients with asymptomatic bacteriuria (55)*		*Matched control obstetric patients†*
	Positive FA tests (26)*	*Negative FA tests (29)*	*(55)*
BUN (mg./100 ml.)			
Mean	8.5	8.5	N.D.‡
Median	8.5	8.0	N.D.
Range	4.0-17.0	5.0-15.0	N.D.
Standard error	±0.5	±0.4	
Standard deviation	±2.6	±1.9	
Serum creatinine (mg./100 ml.)			
Mean	0.85	0.76	0.73
Median	0.85	0.80	0.70
Range	0.5-1.2	0.6-1.1	0.5-1.0
Standard error	±0.04	±0.02	±0.02
Standard deviation	±0.19	±0.11	±0.11
24 Hour creatinine clearance (ml./min.)			
Mean	96	118	129
Median	90	112	124
Range	55-170	85-180	86-186
Standard error	±4.6	±4.1	±3.4
Standard deviation	±23.5	±22.3	±25.5

*FA = Immunofluorescent test for presence of antibody-coated bacteria in urinary sediment.
†Patients with negative urine cultures and without history of urinary tract infection.
‡N.D. = Not done.

use of fluorescein-conjugated anti-human globulin of horse origin.* Serum antibody titers against the patient's own infecting bacteria were determined by indirect immunofluorescence.[1] Saline controls and normal human serum controls were included in each test.

Standard renal function tests were performed as soon as possible after confirmation of asymptomatic bacteriuria. The AutoAnalyzer† was used to determine the blood urea nitrogen (BUN), serum creatinine, and 24 hour urine creatinine. For purposes of comparison, the creatinine clearance value was adjusted to the standard body surface area of 1.73 square meters by calculating each patient's body surface area from her height and weight. The lower limit for normal values of creatinine clearance was considered to be 90 ml. per minute.[5] Creatinine clearance determinations were performed on an equal number of control obstetric patients; the patients were matched by corresponding weeks of gestation, gave no past history of urinary tract infection, and had negative urine cultures.

All patients with asymptomatic bacteriuria were followed in a special "high-risk" obstetric clinic for the remainder of the pregnancy. On each appointment, urine specimens were cultured to detect recurrence of bacteriuria; with each recurrence, FA tests were done, and the patient was treated with appropriate antibiotics. At birth, the infants were examined by the obstetricians and pediatricians for evidence of intrauterine growth retardation (IUGR).* Some of the patients had moved from the area before delivery; each patient was given a copy of her chart, and the new obstetrician was also contacted by mail.

Results

Of the 1,400 obstetric patients screened for bacteriuria at the initial clinic appointment, 70 (5 per cent) had confirmed asymptomatic bacteriuria, and FA tests for antibody-coated bacteria were positive on specimens from 35 (50 per cent) of these patients. The majority of bacterial isolates were *Escherichia coli* (49 patients, 70 per cent) and *Klebsiella pneumoniae* (10 patients, 14 per cent). Other isolates included: Proteus, three; Enterobacter, three; Citrobacter, one; Streptococcus, three; and Staphlococcus, one.

Renal function tests were performed during the

*Roboz Surgical Instrument Company, Washington, D. C.
†Technicon II, Technicon Corp., Tarrytown, New York 10591.

*IUGR for single-birth infants—the infant's weight is below the tenth percentile of this hospital's "normal-weight" infant for the corresponding gestational age.[6, 7]

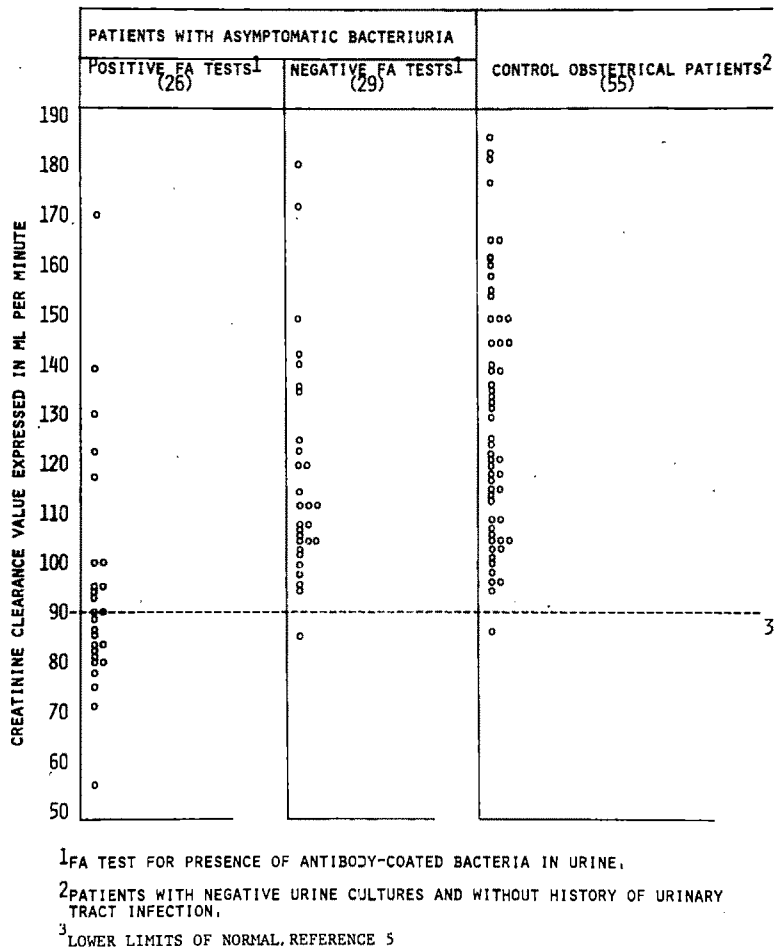


Fig. 1. Creatinine clearance values in 55 obstetric patients with asymptomatic bacteriuria.

second and third trimesters—as soon as possible after the initial appointment. The test results, available for 55 of the 70 patients, were compared with the results of FA tests (Table I). Analysis of variance was utilized to evaluate the renal function data. The comparison of the mean, median, range, standard error, and standard deviation for the BUN values demonstrated that there was no significant difference ($p > 0.05$) for asymptomatic bacteriuric patients regardless of the results of FA tests. Serum creatinine values for 26 bacteriuric patients with positive FA tests were compared to values for 29 patients with negative FA tests and to values for 55 matched control obstetric patients. There was a significant difference ($p < 0.05$) between the FA-positive (mean and median 0.85 and range 0.5 to 1.2 mg. per 100 ml.) and the FA-negative (mean 0.76, median 0.80, and range 0.6 to 1.1 mg. per 100 ml.) groups and between the FA-positive and control (mean 0.73, median 0.70, and range 0.5 to 1.0 mg. per 100 ml.) groups. There was no significant difference ($p > 0.05$) between the FA-negative and control groups. Results of 24 hour creatinine clearance studies showed significant differences ($p < 0.05$). The creatinine clearance values for the FA-positive group (mean 96, median 90, and range 55 to 170 ml. per minute) were significantly different ($p < 0.05$) from those for both the FA-negative group (mean 118, median 112, and range 85 to 180 ml. per minute) and the control group (mean 129, median 124, and range 86 to 186 ml. per minute). The creatinine clearance values for the FA-negative group were also significantly different ($p < 0.05$) from those obtained for the control group.

The creatinine clearance for 15 of 26 patients with positive FA tests (58 per cent) was <90 ml. per minute, while only one of 29 patients with negative FA tests (3 per cent) and only one of the 55 control patients (2 per cent) had such low creatinine clearance values (Fig. 1). The one patient with a negative FA test and creatinine clearance of <90 ml. per minute subsequently had a recurrence of asymptomatic bacteriuria; the FA test became positive.

Table II. IUGR associated with maternal asymptomatic bacteriuria

	Maternal data						*Infant data*		
*Patient**	*Week of pregnancy bacteriuria was detected*	*FA† test for antibody-coated bacteria in urine*	*Serum antibody titer‡*	*Creatinine clearance (c.c./min.)*	*Rise in diastolic blood pressure§ (mm./Hg)*	*Weeks' duration of pregnancy‖*	*Average expected weight¶ (grams)*	*Weight below tenth percentile¶ (grams)*	*Infant's actual weight (grams)*
T. G.	37	Positive	1,024	88	60 to 120	40	3,250	2,590	2,155
M. I.	32	Positive	512	83	50 to 80	41	3,500	2,650	2,645
N. B.	23	Positive	256	95	60 to 70	42	4,001	2,700	2,410
J. R.	12	Positive	32	74	60 to 90	42	4,001	2,700	2,608

*M. I. was previously delivered of two term infants with IUGR (2,353 and 2,381 grams). T. G., N. B., and J. R. were primigravid. Recurrence of bacteriuria during gestation occurred in T. G. and J. R. Albuminuria was present at delivery in T. G.

†FA = Immunofluorescent test for presence of antibody-coated bacteria in urinary sediment.

‡Indirect fluorescent antibody method with results expressed as reciprocal of serum dilution end point.

§Rise in diastolic blood pressure from initial visit to delivery.

‖Patients (T. G. and M. I.) transferring to our center late in gestation had accurate antenatal records documenting the duration of pregnancy.

¶Average expected weight and weight below tenth percentile.[6, 7]

For 57 of the 70 patients with bacteriuria, serum antibody titers were determined against their own infecting microorganisms. Only eight of 57 patients (14 per cent) had serum antibody titers of ≥512, i.e., titers considered to be significant.[1] Each of these eight patients had positive FA tests for the presence of antibody-coated bacteria. All the other patients, 24 with positive FA tests and 25 with negative FA tests, had serum antibody titers comparable to those of normal control sera (ranging from 32 to 256).

Bacteriuria recurred in 10 of the 35 patients with positive FA tests (29 per cent). These 10 patients experienced a total of 14 reinfections (including one case of symptomatic cystitis) without relapses; all the FA tests were negative. Eight of the 35 patients with negative FA tests (23 per cent) experienced 10 episodes of recurrent bacteriuria. Eight of the episodes were reinfections (the FA tests were negative in four and positive in four), and two of the episodes were relapse infections (the FA test was negative in one and positive in the other). The five patients with recurring bacteriuria and positive FA tests originally had creatinine clearance values less than the median for the group.

Four patients were noted to have progression of urinary tract infection. Prior to antibiotic therapy, two asymptomatic patients, with positive FA tests, were hospitalized with symptomatic pyelonephritis. Two other asymptomatic patients with initially negative FA tests subsequently developed symptomatic pyelonephritis.

For patients delivered of their infants at our hospital, the outcome of the pregnancy was compared in groups, i.e., FA-positive bacteriuria, FA-negative bacteriuria, and nonbacteriuria. Infants of 53 mothers with bacteriuria were compared to the infants of 1,330 mothers without bacteriuria* as to birth weight, prematurity, and IUGR. Minimal differences were found between the median weight of infants of the 26 mothers with positive FA tests (7 pounds, 5 ounces—3,310 grams), the 27 mothers with negative FA tests (7 pounds, 7 ounces—3,375 grams), and the 1,330 mothers without bacteriuria (7 pounds, 8 ounces—3,402 grams). Premature infants (i.e., delivered 21 days or more prior to estimated date of delivery with corresponding weight for gestational age) were born to three of the 53 bacteriuric mothers (5.7 per cent); one mother had a positive FA test, and two mothers had negative tests. Thirty-nine premature infants (2.9 per cent) were born to the 1,330 obstetric patients without bacteriuria.

A strict definition for IUGR, i.e., infant weight below the tenth percentile of "normal" weight for the gestational age, was used to differentiate the premature from the IUGR infant. Four of the 53 mothers with asymptomatic bacteriuria (7.5 per cent) gave birth to infants with IUGR (Table II). Each of these four mothers had a positive FA test. For the remaining 1,330 obstetric patients with negative urine cultures, 21 infants (1.6 per cent) had IUGR. Two of the 21 patients who were delivered of infants with IUGR had a history of renal disease, although their urine cultures were repeatedly negative during the gestation.

*As a patient moved from the area, a new nonbacteriuric obstetric control patient replaced her in the analysis to retain a total of 1,330 patients without bacteriuria.

Comment

The site of urinary tract infection in patients with asymptomatic bacteriuria may be localized by ureteral catheterization, not a procedure to be performed routinely during pregnancy. With ureteral catheterization in patients with asymptomatic bacteriuria, renal bacteriuria was found by Fairly and associates[8] in 22 of 50 pregnant women (44 per cent) and by Whalley and colleagues[9] in 17 of 23 postpartum women (73 per cent). The immunofluorescence test for detecting antibody-coated bacteria is a simple and reliable method for localizing the site of urinary tract infection.[1, 2] In addition, antibody-coated bacteria are associated with acute kidney infections during pregnancy.[3] With the use of the FA test for antibody-coated bacteria in this series, the site of asymptomatic bacteriuria was shown to be of renal origin in 35 of 70 pregnant patients (50 per cent). Thus, we believe that the noninvasive, reliable, and simple FA test can be used routinely in pregnant women with asymptomatic bacteriuria to determine the site of infection.

We wanted to determine whether results of renal function studies correlated with results of FA tests in the patients with asymptomatic bacteriuria. We confirmed the findings of Kaitz[10] that patients with bacteriuria have a lower mean creatinine clearance value than the nonbacteriuric patients. Doolan and co-workers[5] reported for nonpregnant women that the normal range of actual values for creatinine clearance was 87 to 107 ml. per minute per 1.73 sq.M., and the value for true creatinine clearance was 98 to 130 ml. per minute per 1.73 sq. M. Glomerular filtration rate increases during pregnancy, and normal values for creatinine clearance for pregnant women range from 125 to 200 ml. per minute per 1.73 sq. M.[11, 12] In the present study, actual values of creatinine clearance were used, and values of <90 ml. per minute per 1.73 sq. M. were accepted as being definitely abnormal for pregnant patients. Significant differences ($p < 0.05$) were noted between the 24 hour creatinine-clearance determinations for the patients with positive FA tests and those with negative FA tests. Fifty-eight per cent of the patients with positive FA tests (upper-tract infection) as compared to 3 per cent of the patients with negative FA tests (lower-tract infection) had creatinine clearance values of <90 ml. per minute. Whalley and co-workers[11] reported that 25 per cent of patients with acute pyelonephritis develop transient, but definite, decreases in creatinine-clearance values (<80 ml. per minute). For obstetric patients with silent renal parenchymal infection, we also found a significant decrease ($p < 0.05$) in the glomerular filtration rate. The median creatinine-clearance values were 90 ml. per minute for patients with positive FA tests, 112 ml. per minute for those with negative FA tests, and 124 ml. per minute for control subjects (Table I). Five of 17 patients with negative FA tests and creatinine-clearance values less than the median (112 ml. per minute) had a recurrence of bacteriuria; the FA tests became positive.

The wide ranges and overlapping of the creatinine-clearance values for the nonbacteriuric and bacteriuric patients indicate that this test should not be used for localizing the site of infection for an individual patient (Fig. 1 and Table I). In contrast, the FA test does localize the site of infection. Furthermore, on the basis of our data, the FA test allows selection of those bacteriuric patients with upper-tract infection who need further renal evaluation.

The effects of urinary tract infections upon the outcome of pregnancy have been discussed by previous investigators.[7, 13–18] In studying the outcome of the gestation in relation to the results of the FA test in our asymptomatic bacteriuric patients, we distinguished between the "normal-weight" premature infant and the low–birth-weight infant resulting from IUGR. The incidence of IUGR for infants born to mothers with positive FA tests was four of 27 (15 per cent); 21 of the 1,330 nonbacteriuric patients (1.6 per cent) were delivered of infants with IUGR. Thus, at this medical center the incidence of IUGR in the infants born to mothers with positive FA tests was nine times greater than the expected incidence for nonbacteriuric mothers. The four patients who gave birth to infants with IUGR had evidence of renal disease as indicated by: (1) positive FA tests (four patients), (2) creatinine-clearance values lower than the mean for patients with positive FA tests (four patients), (3) elevations of at least 30 mm. of mercury in diastolic blood pressure during the gestation (three patients), (4) elevated serum antibody titers (two patients), and (5) recurrence of bacteriuria (two patients).

Thus, the FA test provides a new approach to the problem of asymptomatic bacteriuria during pregnancy. This test is a reliable, safe procedure for localizing the site of urinary tract infection. The finding of a positive FA test, signifying upper-tract infection, selects the patient who needs renal function evaluation and alerts the clinician to the increased risk that the patient will be delivered of an intrauterine–growth-retarded infant.

We thank Mr. Gabriel Hui for his technical assistance, and we appreciate the interest and cooperation of the Wilford Hall Medical Center Obstetrical staff and Nursing staff.

REFERENCES

1. Thomas, V. L., Shelokov, A., and Forland, M.: Antibody-coated bacteria in the urine and the site of urinary tract infection, N. Engl. J. Med. **290:** 588, 1974.
2. Jones, S. R., Smith, J. W., and Sanford, J. P.: Localization of urinary tract infections by detection of antibody-coated bacteria in urine sediment, N. Engl. J. Med. **290:** 591, 1974.
3. Thomas, V. L., Harris, R. E., Gilstrap, L. C., III, and Shelokov, A.: Antibody-coated bacteria in urines from obstetrical patients with acute pyelonephritis, J. Infect. Dis. **131:** S57, 1975.
4. Hoeprich, P. D.: Culture in urine, J. Lab. Clin. Med. **56:** 899, 1960.
5. Doolan, P. D., Alpen, E. L., and Theil, G. B.: A clinical appraisal of the plasma concentration and endogenous clearance of creatinine, Am. J. Med. **32:** 65, 1962.
6. Lubechenco, L. O., Hansman, C., and Boyd, E.: Intrauterine growth in length and head circumference as estimated from livebirths at gestational ages from 26 to 42 weeks, Pediatrics **37:** 403, 1966.
7. Perry, C. P., Harris, R. E., DeLemos, R. A., and Null, D. M.: Intrauterine growth retarded infants: Correlation of gestational age with maternal factors, mode of delivery and fetal and neonatal survival, Obstet. Gynecol. Accepted for publication.
8. Fairley, K. F., Bond, A. G., and Adey, F. D.: The site of infection in pregnancy bacteriuria, Lancet **1:** 939, 1966.
9. Whalley, P. J., Martin, F. G., and Peters, P. C.: Significance of asymptomatic bacteriuria detected during pregnancy, J. A. M. A. **193:** 879, 1965.
10. Kaitz, A. L.: Urinary concentrating ability in pregnant women with asymptomatic bacteriuria, J. Clin. Invest. **40:** 1331, 1961.
11. Whalley, P. J., Cunningham, F. G., and Martin, F. G.: Transient renal dysfunction associated with acute pyelonephritis of pregnancy, Obstet. Gynecol. **46:** 174, 1975.
12. Sims, E. A. H., and Krantz, K. E.: Serial studies of renal function during pregnancy and the puerperium in normal women, J. Clin. Invest. **37:** 1764, 1958.
13. Harris, R. E., and Gilstrap, L. C., III: Prevention of recurrent pyelonephritis during pregnancy, Obstet. Gynecol. **44:** 637, 1974.
14. Kass, E. H.: Bacteriuria and pyelonephritis of pregnancy, Arch. Intern. Med. **105:** 194, 1960.
15. Kass, E. H.: Pyelonephritis and bacteriuria: A major problem in preventive medicine. Ann. Intern. Med. **56:** 46, 1962.
16. Kincaid-Smith, P., and Bullen, M.: Bacteriuria in pregnancy, Lancet **1:** 395, 1965.
17. Little, P. H.: The incidence of urinary infection in 5,000 pregnant women, Lancet **2:** 925, 1966.
18. Wilson, M. G., Hewitt, W. J., and Monzon, O. T.: Effect of bacteriuria on the fetus, N. Engl. J. Med. **274:** 1115, 1966.

Obstetric Anesthesia Conference

The Sixth Obstetric Anesthesia Conference, sponsored by the Los Angeles Obstetrical and Gynecological Society, will be held in Los Angeles on March 25, 26, and 27, 1977, and then continue for Part II which will be at Del Webb's Kuilima resort hotel on the north shore of Oahu, Hawaii. The dates for the second part will be March 28 through 31, 1977.

The meetings are planned in the late afternoon to give everyone time to enjoy the great Hawaii weather and the many activities available such as tennis, golf, snorkeling, sightseeing, or just relaxing in the sun.

This year's speakers include Drs. John J. Bonica, John G. P. Cleland, Roger K. Freeman, Charles P. Gibbs, Bradley E. Smith, Richard B. Clark, Watson Bowes, Toshio Akamatsu, and John S. McDonald. Lectures are planned with the total perinatal period emphasized from the obstetric, anesthesia, and pediatric viewpoints.

A complete program or further information can be obtained by writing: John S. McDonald, M.D., Obstetric Anesthesia, P. O. Box 7632, Fresno, California 93727. Telephone: (209) 251-4833, Ext. 2228.

Systolic time intervals in normotensive and hypertensive human pregnancy

Y. L. LIM, B.MED.SC., M.B., B.S.*
W. A. W. WALTERS, M.B., B.S., PH.D., F.R.C.O.G., F.A.G.O.
Melbourne, Victoria, Australia

Systolic time intervals were measured in 10 nonpregnant, 37 normotensive, and 18 hypertensive pregnant women in both supine and lateral positions. With all the subjects in the supine position, left ventricular ejection time (LVET) was shortened; the pre-ejection period (PEP) lengthened, and the PEP/LVET ratio increased in normotensive late pregnancy compared with the nonpregnant state. Similar alterations in systolic time intervals were observed in hypertensive women in both early and late pregnancy in the supine position. In normotensive women in early pregnancy, alterations in systolic time intervals were inconclusive. When normotensive women in late pregnancy were turned from the supine into the left lateral position, a prolongation of LVET and a decrease in the PEP/LVET ratio were observed. When hypertensive women in late pregnancy adopted the left lateral position, no significant alterations in systolic time intervals occurred. Isovolumetric contraction time (ICT) was prolonged only in the hypertensive pregnant women in the supine position. The study suggests that left ventricular performance is diminished in normotensive women in late pregnancy when supine but improves when they adopt the lateral position. In addition, hypertensive pregnant women show evidence of diminished left ventricular performance which is not improved in late pregnancy by assumption of the left lateral position.

THE ANALYSIS OF systolic time intervals has proved to be a satisfactory and simple method of studying left ventricular performance in man. Technically, the noninvasive nature of the method allows repeated recordings to be made under physiologic conditions, and its validity has been established by comparison with cardiac catheterization methods.[1–3] One of the most striking physiologic adjustments to human pregnancy is an increase in cardiac output, which is mainly due to an increase in stroke volume.[4–6] In addition, significant changes in left ventricular performance indicated by alterations in systolic time intervals have been reported during normal pregnancy which, to some extent, probably reflect the hemodynamic changes observed.[7–9]

From the Department of Obstetrics and Gynaecology, Monash University, Queen Victoria Memorial Hospital.

Received for publication September 9, 1975.

Accepted December 3, 1975.

Reprint requests: Dr. W. A. W. Walters, Department of Obstetrics and Gynaecology, Monash University, Queen Victoria Memorial Hospital, Melbourne, Victoria, Australia.

**Recipient of a Monash University Postgraduate Scholarship.*

The aims of this study were: (1) to verify the changes in systolic time intervals during normal pregnancy, (2) to compare the variations in systolic time intervals between normotensive and hypertensive pregnancies, and (3) to observe the effect of postural changes on systolic time intervals in late pregnancy in both normotensive and hypertensive women.

Subjects and methods

Volunteers for this study were placed into three groups.

Nonpregnant subjects. Ten normal, healthy, nonpregnant women served as control subjects. Their ages ranged from 19 to 27 years, and all had a normal medical history.

Normotensive pregnant subjects. Eighteen women in early pregnancy (<28 weeks) and 19 women in late pregnancy (>28 weeks) were included in this group. Their ages ranged from 16 to 37 years, and all were normal, healthy women lacking a history of cardiovascular disorders. Twenty-one were primigravid.

Hypertensive pregnant women. Eighteen women were in this category, their ages ranging from 14 to 41 years. Five were in early pregnancy, and 13 were in late

pregnancy. Hypertension was defined as a mean brachial arterial blood pressure of 100 mm. Hg (equivalent to 130 mm. Hg systolic pressure and 85 mm. Hg diastolic pressure) or more. No attempt was made to subclassify the subjects according to the etiology of the hypertension. Patients receiving antihypertensive therapy were excluded.

Most of the recordings of heart rate, blood pressure, and systolic time intervals were taken on one occasion in each subject lying supine. However, an average of three serial investigations was made at intervals of four weeks in 11 of the normotensive subjects and six of the hypertensive pregnant subjects in both the supine and left lateral positions.

Subjects were instructed to refrain from exertion, smoking, and ingestion of food and beverages for at least four hours before each investigation, which was carried out after they had rested for 15 minutes. All recordings in each subject were made between 09.00 and 11.00 hours in a quiet room, in which the temperature was maintained constantly at 22° C.

Heart rate was calculated from a one-minute tracing of the electrocardiogram. Brachial arterial blood pressure, measured by indirect sphygmomanometry, was recorded with the aid of a phonocardiograph adapter* and a pressure transducer† connected to a strain-gauge coupler-amplifier-recorder system.‡

The various phases of systole were measured from simultaneous recordings of the phonocardiogram over the apex of the heart or at the left border of the sternum, the external carotid pulse contour, and a standard limb lead of the electrocardiograph that depicts the best Q wave (usually Lead I or Lead II). All recordings were obtained with the VS4 electrocardiograph* adapted with pulse and phonocardiograph modulators, the signals being amplified and recorded on a Type R polychannel dynograph‡ at a paper speed of 100 mm. per second. Fig. 1 shows a typical tracing.

Total electromechanical systole (QS_2) was measured from the onset of ventricular depolarization to the first high-frequency vibration of the aortic component of the second heart sound. Left ventricular ejection time (LVET) was measured from the beginning of the upstroke to the trough of the incisura of the external carotid pulse tracing. The designation S_1S_2 was given to the interval between the first high-frequency components of the first and second heart sounds.

The pre-ejection period (PEP) was derived by

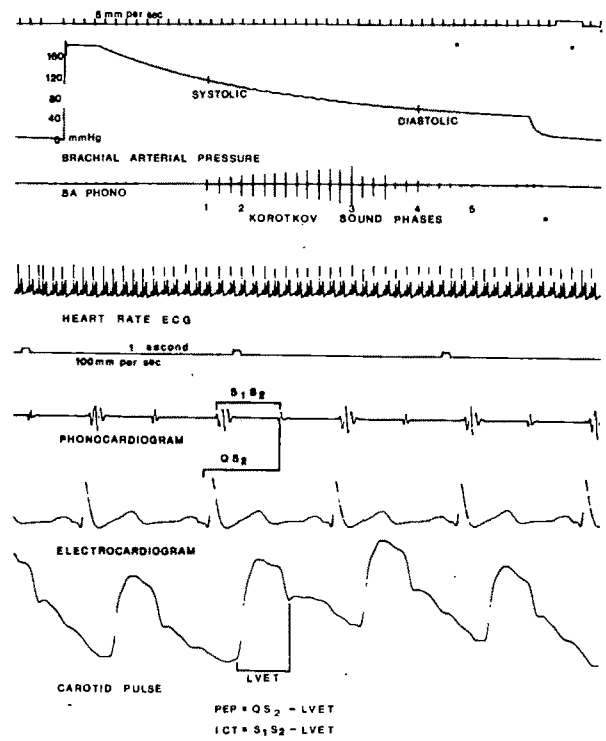


Fig. 1. From top to bottom, actual experimental recordings of brachial arterial pressure by indirect sphygmomanometry, heart rate by electrocardiogram, and simultaneous recordings of phonocardiogram, electrocardiogram, and external carotid pulse contour.

subtracting LVET from QS_2, and the isovolumetric contraction time (ICT) was obtained by subtracting LVET from S_1S_2. The PEP/LVET ratio was also calculated as it has been shown to correlate closely with the ejection fraction of systole and left ventricular end-diastolic pressure and volume.[1, 2]

The final value for each systolic time interval was taken as the mean of 15 to 20 consecutive beats, each read to the nearest 5 msec.

Statistical analysis of the data included determination of the mean and standard deviation for each variable. Systolic time intervals were correlated with the heart rate by Pearson's correlation coefficients. Regression lines of the various systolic time intervals versus heart rate were calculated by the method of "least squares." Comparisons of the slopes and locations of these regression lines were made with the use of the analysis of variance and covariance,[10] while the t test was used to compare values in the supine and lateral positions in both normotensive and hypertensive groups of pregnant women.

Results

Systolic time intervals in the supine position in normotensive and hypertensive pregnant subjects

*Kent Cambridge Instrument Company, Ossining, New York 10562.

†P23Db, Statham Instruments, Inc., 2230 Statham Blvd., Statham Industrial Park, Oxnard, California 93030.

‡Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, California 92634.

Table I. Mean gestational period, brachial arterial blood pressure, and HR in nonpregnant, normotensive, and hypertensive pregnant women in the supine position

Variables	*Nonpregnant control subjects (mean ± 1 S.D.) (No. = 10)*	*Normotensive pregnancy*			
		Early (<28 weeks)		*Late (>28 weeks)*	
		Mean ± 1 S.D. (No. = 18)	*P value*	*Mean ± 1 S.D. (No. = 19)*	*P value*
Mean gestational period (weeks)	—	19 ±5.7	—	33.2 ±4.1	—
Systolic arterial pressure (mm. Hg)	115.0 ±11.0	117.2 ±12.2	>0.2	114.3 ±9.6	>0.2
Diastolic arterial pressure (mm. Hg)	63.2 ±7.0	64.2 ±8.2	>0.2	68.6 ±12.9	>0.2
Mean arterial pressure (mm. Hg)	79.8 ±8.1	81.7 ±7.4	>0.2	84.7 ±9.8	>0.1
HR (beats per minute)	75.3 ±16.7	82.2 ±7.1	>0.1	90.2 ±7.9	<0.01*

*Statistically significant.

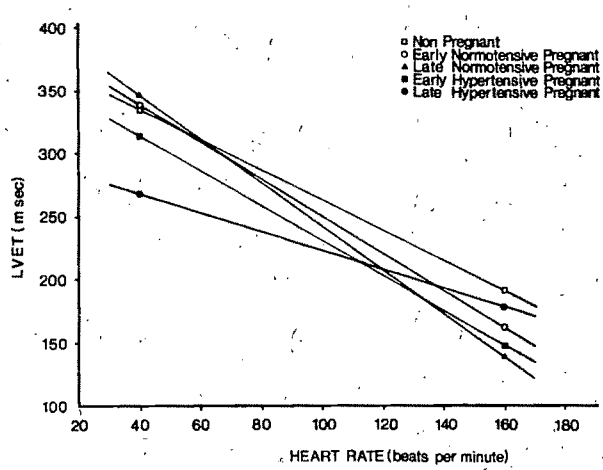


Fig. 2. Regression lines of LVET versus HR in the various experimental groups.

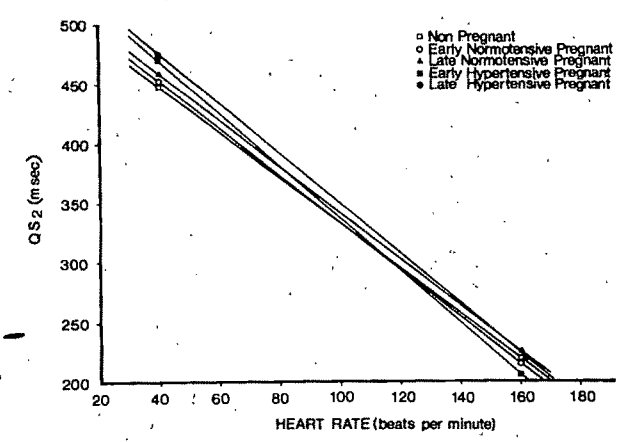


Fig. 3. Regression lines of total QS_2 versus HR in the various experimental groups.

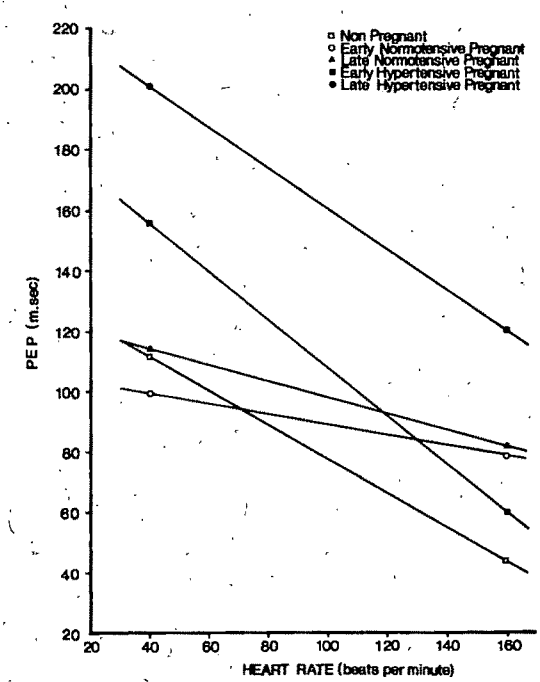


Fig. 4. Regression lines of PEP versus HR in the various experimental groups.

compared with those in normotensive nonpregnant subjects. The mean gestational periods of subjects in early and late pregnancy are listed in Table I. Heart rate was significantly faster in normotensive ($p < 0.01$) and hypertensive ($p < 0.001$) subjects in late pregnancy than in nonpregnant subjects.

According to the classification adopted for the various experimental groups of subjects, systolic, diastolic, and mean arterial blood pressures were significantly different in the hypertensive subjects

Hypertensive pregnancy			
Early (<28 weeks)		*Late (>28 weeks)*	
ean ± 1 S.D. (No. = 5)	*P value*	*Mean ± 1 S.D. (No. = 13)*	*P value*
22.6	—	35.1	—
±5.1		±3.5	
132.0		139.2	
±9.2	<0.02*	±11.8	<0.001*
90.8		93.9	
±5.8	<0.001*	±8.5	<0.001*
104.5		109.6	
±3.5	<0.001*	±7.7	<0.001*
77.2		99.8	
±11.0	>0.2	±12.0	<0.001*

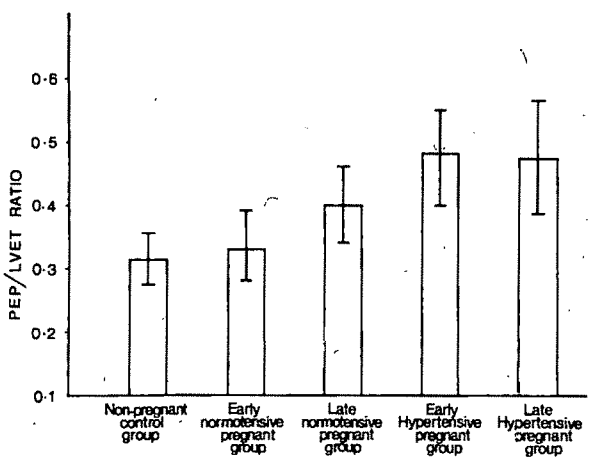


Fig. 5. PEP/LVET ratios with one standard deviation in the various experimental groups.

compared with the normotensive pregnant and nonpregnant subjects (Table I).

Table II summarizes the observed values of LVET, QS_2, PEP, ICT, and PEP/LVET ratios in the supine position in all groups. In the four groups of pregnant subjects, the observed values of LVET, QS_2, and PEP were compared with their predicted values obtained by correcting for differences in heart rate (HR) with the regression equations of the nonpregnant subjects which were as follows: LVET = 383.5 − 1.202 HR ± 23.67 ($r = 0.90$, $p < 0.001$); QS_2 = 517.2 − 1.755 HR ± 35.15 ($r = 0.89$, $p < 0.001$); PEP = 134.0 − 0.56 HR ± 15.78 ($r = 0.63$, $p < 0.05$). These equations do not differ significantly from those reported by Weissler and co-workers.[11]

Regression equations were also calculated for systolic time intervals in the four groups of pregnant subjects, and an analysis of covariance was performed (Table III). Compared with those of nonpregnant subjects, the regression lines for the various systolic time intervals plotted against the HR did not differ in their slopes. This suggests that LVET, QS_2, and PEP vary with the heart rate in the same manner in all groups of subjects. However, regression lines for LVET and PEP in normotensive subjects in late pregnancy and in hypertensive subjects in both early and late pregnancy differed in their locations when compared with those of nonpregnant subjects.

LVET was shorter for any given heart rate in normotensive subjects in late pregnancy ($p < 0.05$) and in hypertensive subjects in both early and late pregnancy ($p < 0.05$ and $p < 0.001$, respectively) than in nonpregnant subjects (Fig. 2). Total electromechanical systole varied with the HR in the same manner, and the observed values did not differ significantly in all five groups of subjects (Fig. 3).

The PEP was significantly longer in normotensive subjects in late pregnancy ($p < 0.001$) and in hypertensive subjects in early and late pregnancy ($p < 0.02$ and $p < 0.001$, respectively) than in nonpregnant subjects (Fig. 4).

ICT remained unaltered in the nonpregnant and normotensive pregnant subjects but was significantly prolonged in the two groups of hypertensive pregnant subjects ($p < 0.02$). The ratios of PEP/LVET were 0.314 and 0.331 in the nonpregnant and normotensive subjects in early pregnancy, respectively. The ratio was significantly increased to 0.403 ($p < 0.01$) in normotensive subjects in late pregnancy and to 0.476 ($p < 0.001$) and 0.470 ($p < 0.001$) in hypertensive subjects in early and late pregnancy, respectively (Fig. 5).

The effects of postural change on systolic time intervals in normotensive and hypertensive subjects in late pregnancy (Table IV). Heart rate and blood pressure did not alter significantly when normotensive or hypertensive pregnant subjects were turned from the supine into the left lateral position. In the normotensive pregnant subjects, however, significant lengthening of QS_2 ($p < 0.01$) and LVET ($p < 0.01$) was observed when the left lateral position was adopted. As a result of the lengthened LVET, the PEP/LVET ratio was significantly reduced from 0.391 to 0.339 ($p < 0.02$).

These alterations in systolic time intervals in response to postural change were not observed in the hypertensive pregnant subjects.

Table II. Observed and predicted systolic time intervals in nonpregnant, normotensive, and hypertensive pregnant women in the supine position

Variables	Observed value in nonpregnant group (No. = 10)	Normotensive pregnancy					
		Early (<28 weeks)			Late (>28 weeks)		
		Observed mean ± 1 S.D. (No. = 18)	Predicted mean ± 1 S.D. (No. = 18)	P value	Observed mean ± 1 S.D. (No. = 19)	Predicted mean ± 1 S.D. (No. = 19)	P value
LVET (msec.)	293 ±22	276 ±18	284 ±9	>0.2	257 ±20	275 ±9	<0.05*
QS_2 (msec.)	385 ±33	367 ±19	372 ±13	>0.2	357 ±21	358 ±14	>0.2
PEP (msec.)	92 ±15	91 ±12	88 ±4	>0.2	101 ±11	84 ±4	<0.00
ICT (msec.)	39 ±14	39 ±12	—	>0.2	44 ±12	—	>0.2
PEP/LVET	0.314 ±0.042	0.331 ±0.052	—	>0.2	0.403 ±0.063	—	<0.01*

*Statistically significant.

Table III. Covariant analysis of regression lines of normotensive and hypertensive pregnant groups compared with the nonpregnant group

Variables (Y)	Experimental Group	Difference in regression lines				Differences in variables (DY) corrected for HR (DY = Y nonpregnant − Y pregnant)	
		Slope	P Value	Location	P Value		
LVET	Early normotensive	0.2478	>0.2	9.255	>0.05	DY = −10.65 + 0.2478	HR
	Late normotensive	0.5054	>0.2	15.954	<0.05*	DY = −27.42 + 0.5054	HR
	Early hypertensive	0.1909	>0.2	27.658	<0.001*	DY = 12.979 + 0.1909	HR
	Late hypertensive	−0.671	>0.05	34.46	<0.001*	DY = 94.66 − 0.6707	HR
QS_2	Early normotensive	0.2001	>0.2	5.126	>0.2	DY = −10.95 + 0.2001	HR
	Late normotensive	0.2779	>0.2	0.3660	>0.2	DY = −23.49 + 0.2779	HR
	Early hypertensive	0.4409	>0.2	−6.471	>0.2	DY = −40.37 + 0.4409	HR
	Late hypertensive	0.3495	>0.2	−8.137	>0.2	DY = −39.51 + 0.3495	HR
PEP	Early normotensive	−0.391	>0.2	−2.043	>0.2	DY = 29.35 − 0.391	HR
	Late normotensive	−0.296	>0.2	−15.48	<0.01*	DY = 9.93 − 0.2961	HR
	Early hypertensive	0.2422	>0.2	−33.94	<0.001*	DY = −52.66 + 0.2422	HR
	Late hypertensive	1.0124	<0.05*	−42.51	<0.001*	DY = −133.3 + 1.0124	HR

*Statistically significant.

Comment

In this study, the alterations in systolic time intervals during normotensive pregnancy are similar to those reported by Burg and associates[8] and Liebson and associates.[9] In the supine position, significant lengthening of the PEP was observed in late pregnancy, associated with a shortening of LVET and consequently an increase in the PEP/LVET ratio.

Since LVET is directly related to stroke volume,[11, 12] its diminution in subjects in late pregnancy lying supine indicates a reduction in stroke volume. The mechanism of this is probably a decrease in venous return secondary to partial or complete occlusion of the inferior vena cava by the enlarged uterus.[13, 14] The finding of a prolonged LVET in the same subjects when they adopted the left lateral position reflects an increase in venous return and cardiac output consequent upon release of the caval occlusion.[14, 15]

The PEP includes the activation of the heart and the period of pressure rise in the left ventricle up to the time of opening of the aortic valves. As the rate of pressure rise in the left ventricle increases, the PEP decreases.[16] Enhancement of left ventricular performance in the left lateral position in normotensive women in late pregnancy is suggested by a shortened PEP and ICT with a diminished PEP/LVET ratio. In this position, the improved venous return results in an increase in end-diastolic volume and lengthening of

Hypertensive pregnancy					
Early (<28 weeks)			*Late (>28 weeks)*		
Observed mean ± 1 S.D. (No. = 5)	*Predicted mean ± 1 S.D. (No. = 5)*	*P value*	*Observed mean ± 1 S.D. (No. = 13)*	*Predicted mean ± 1 S.D. (No. = 13)*	*P value*
263 ±16	290 ±13	<0.05*	235 ±15	263 ±14	<0.001*
388 ±29	378 ±20	>0.2	346 ±31	337 ±22	>0.2
125 ±20	91 ±6	<0.02*	111 ±24	78 ±7	<0.001*
67 ±14	—	<0.02*	60 ±19	—	<0.02*
0.476 ±0.078	—	<0.001	0.470 ±0.095	—	<0.001*

Table IV. Changes in brachial arterial blood pressure, HR, and systolic time intervals in normotensive and hypertensive women in late pregnancy when turned from a supine to a left lateral position

Variable	*Normotensive pregnancy*		*P value*	*Hypertensive pregnancy*		*P value*
	Supine (mean ± 1 S.D.) (No. = 11)	*Left lateral (mean ± 1 S.D.) (No. = 11)*		*Supine (mean ± 1 S.D.) (No. = 6)*	*Left lateral (mean ± 1 S.D.) (No. = 6)*	
Mean gestational period (weeks)	32.3 ±2.9	32.3 ±2.9	—	36.2 ±3.9	36.2 ±3.9	—
Systolic arterial pressure (mm. Hg)	108.8 ±7.5	113.6 ±8.4	>0.1	135.6 ±17.2	143.6 ±13.2	>0.2
Diastolic arterial pressure (mm. Hg)	67.7 ±8.8	67.6 ±11.9	>0.2	86.6 ±13.9	98.8 ±12.2	>0.1
Mean arterial pressure (mm. Hg)	81.9 ±8.4	83.3 ±9.0	>0.2	103.1 ±13.9	113.7 ±7.7	>0.1
HR (beats per minute)	86.9 ±7.1	84.6 ±8.2	>0.2	95.3 ±12.0	93.0 ±10.2	>0.2
LVET (msec.)	250 ±14	275 ±25	<0.01*	245 ±29	247 ±24	>0.2
QS_2 (msec.)	347 ±14	368 ±16	<0.01*	349 ±30	356 ±24	>0.2
PEP (msec.)	97 ±10	93 ±4	>0.2	104 ±15	109 ±15	>0.2
ICT (msec.)	41 ±12	38 ±7	>0.2	52 ±12	52 ±12	>0.2
PEP/LVET	0.391 ±0.049	0.339 ±0.052	<0.02*	0.429 ±0.082	0.446 ±0.080	>0.2

*Statistically significant.

myocardial fibers. Furthermore, the release of aortic compression by the gravid uterus in the left lateral position would contribute to better left ventricular performance by reducing aortic impedance.

While Burg and his co-workers[8] found the PEP and LVET to be shortened in the first and second trimesters of normal pregnancy, this study did not reveal any significant changes in systolic time intervals at these periods of gestation. Such a discrepancy could partly be accounted for by the difference in grouping of subjects according to gestational age in the two studies.

Systolic time intervals remain fairly constant with variations of blood pressure within the normal range.[11]

Furthermore, among patients with chronic arterial hypertension causing minimal functional impairment, no independent effect of arterial blood pressure on the systolic time intervals or PEP/LVET ratio could be demonstrated.[12]

However, PEP correlates with alterations in

peripheral resistance and increases with rising diastolic pressure and diminishing stroke volume.[17]

In hypertensive subjects investigated in the supine position in early and late pregnancy, shortening of LVET and lengthening of the PEP and ICT were observed with consequent increase in the PEP/LVET ratio.

These findings are consistent with an increase in aortic pressure, resulting in earlier closure of the aortic valves. No significant differences in systolic time intervals were found when hypertensive subjects in late pregnancy were turned from the supine into the left lateral position. A number of factors present in hypertensive states associated with pregnancy may be responsible, including diminished plasma volume,[18] increased aortic input impedance, reduced functional response of the myocardium to alterations in ventricular end-diastolic fiber length and volume, and changes in aortic wall distensibility. In addition, the left ventricle in the hypertensive subjects might be somewhat less compliant and, therefore, less sensitive to minor alterations in preload. From hemodynamic and biochemical aspects, the left lateral position in late pregnancy and labor is probably more favorable than the supine position for both mother and fetus.[14, 18] The alterations in systolic time intervals in normotensive pregnant women revealed in this study provide further evidence in favor of the lateral position.

We are grateful to Professor Carl Wood, Dr. Allan Chang, Miss Lyndall Shields, Mr. Peter Trigg, and Mrs. Zoe Snowdon for advice and assistance with various aspects of the work. Our thanks are also due to the consultant obstetricians of the Queen Victoria Memorial Hospital, Melbourne, who allowed us to investigate patients under their supervision, and above all to the patients who volunteered.

REFERENCES

1. Ahmed, S. S., Levinson, G. E., Schwartz, C. J., and Ehinger, P. O.: Comparison of systolic time intervals with direct measures of myocardial contractility in man, Clin. Res. **18:** 294, 1970.
2. Garrard, C. L., Jr., Weissler, A. M., and Dodge, H. T.: The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease, Circulation **42:** 455, 1970.
3. Martin, C. E., Shaver, J. A., Thompson, M. E., Reddy, P. S., and Leonard, J. J.: Direct correlation of external systolic time intervals with internal indices of left ventricular function in man, Circulation **44:** 419, 1971.
4. Adams, J. Q.: Cardiovascular physiology in normal pregnancy. Studies with dye dilution technique, AM. J. OBSTET. GYNECOL. **67:** 741, 1954.
5. Rovinsky, J. J., and Jaffin, H.: Cardiovascular hemodynamics in pregnancy. III. Cardiac rate, stroke volume, total peripheral resistance, and central blood volume in multiple pregnancy. Synthesis of results, AM. J. OBSTET. GYNECOL. **95:** 787, 1966.
6. Walters, W. A. W., MacGregor, W. G., and Hills, M.: Cardiac output at rest during pregnancy and the puerperium, Clin. Sci. **30:** 1, 1966.
7. Rubler, S., Schneebaum, R., and Hammer, N.: Systolic time intervals in pregnancy and the postpartum period, Am. Heart J. **86:** 182, 1973.
8. Burg, J. R., Dodek, A., Kloster, F. E., and Metcalfe, J.: Alterations of systolic time intervals during pregnancy, Circulation **49:** 560, 1974.
9. Liebson, P. R., Mann, L. I., Evams, M. I., Duchin, S., and Arditi, L.: Cardiac performance during pregnancy: Serial evaluation using external systolic time intervals, AM. J. OBSTET. GYNECOL. **122:** 1, 1975.
10. Armitage, P.: Statistical Methods in Medical Research, Oxford, 1971, Blackwell Scientific Publications, p. 281.
11. Weissler, A. M., Harris, W. S., and Schoenfeld, C. D.: Systolic time intervals in heart failure in man, Circulation **37:** 149, 1968.
12. Weissler, A. M., Peeler, R. G., and Roehll, W. H., Jr.: Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease, Am. Heart J. **62:** 367, 1961.
13. Kerr, M. G., Scott, D. B., and Samuel, E.: Studies of the inferior vena cava in late pregnancy, Br. Med. J. **1:** 532, 1964.
14. Ueland, K., Novy, M. J., Peterson, E. N., and Metcalfe, J.: Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise, AM. J. OBSTET. GYNECOL. **104:** 856, 1969.
15. Vorys, N., Ullery, J. C., and Hanusek, G. E.: The cardiac output changes in various positions in pregnancy, AM. J. OBSTET. GYNECOL. **82:** 1312, 1961.
16. Metzger, C. C., Chough, C. B., Kroetz, F. W., and Leonard, J. J.: True isovolumic contraction time. Its correlation with two external indices of ventricular performance, Am. J. Cardiol. **25:** 434, 1970.
17. Winters, W. G., Leaman, D. M., and Anderson, R. A.: The effect of exercise on intrinsic myocardial performance, Circulation **48:** 50, 1973.
18. Chesley, L. C.: Plasma and red cell volume during pregnancy, AM. J. OBSTET. GYNECOL. **112:** 440, 1972.
19. Humphrey, M. D., Chang, A., Wood, E. C., Morgan, S., and Hounslow, D.: A decrease in fetal pH during the second stage of labour, when conducted in the dorsal position, J. Obstet. Gynaecol. Br. Commonw. **81:** 600, 1974.

The relationship of hospital-acquired maternal infection to invasive intrapartum monitoring techniques

CHARLES B. GASSNER, M.D.
WILLIAM J. LEDGER, M.D., F.A.C.O.G.
Los Angeles, California

A 6 month survey of hospital-acquired uterine infection was done on the obstetric service of the Los Angeles County–University of Southern California (LAC-USC) Medical Center to determine the impact of the duration of monitoring upon the incidence of maternal infection. There were significantly more infections among the population monitored and in women undergoing cesarean section. In diminishing order, the incidence of infection was: cesarean section monitored, 90 ot 223 (40.4 per cent); cesarean section not monitored, 56 ot 271 (20.4 per cent); elective repeat cesarean section, 1 of 21 (5 per cent); vaginal delivery monitored, 33 of 1,236 (2.7 per cent); and vaginal delivery not monitored, 49 of 3,445 (1.4 per cent). In comparing those patients with infection and those free of infection following equivalent routes of delivery, there was no statistical difference in the duration of monitoring. These results suggest that the interval of monitoring alone is not a significant clinical factor in the development of maternal soft-tissue pelvic infection in a high-risk obstetric population.

MODERN PERINATAL research has produced a variety of invasive techniques which provide more accurate assessment of the fetus and the mother during labor. Continuous monitoring of the fetal heart rate by signals produced by a fetal electrocardiogram and a direct measure of intraamniotic fluid pressure are both widely used in clinical obstetric services. Their increased precision over conventional methods of palpation and ausculation has been well documented.[1] The transcervical application of a fetal scalp electrode and the introduction of an intrauterine pressure catheter require prior rupture of the membranes, either spontaneous or induced. This indwelling equipment provides a possible route for the entry of bacteria from the vagina and endocervix into the amniotic fluid with the potential of a resultant amnionitis and/or a postpartum endomyometritis. This study was undertaken to evaluate the risk of the duration of these monitoring procedures for a population of women from lower socioeconomic classes in a large urban hospital, the Los Angeles County–University of Southern California (LAC-USC) Medical Center.

From the Department of Obstetrics-Gynecology, Los Angeles County–University of Southern California Medical Center.

Received for publication August 29, 1975.

Revised January 12, 1976.

Accepted January 22, 1976.

Reprint requests: William J. Ledger, M.D., LAC-USC Medical Center, Women's Hospital, 1240 North Mission Rd., Los Angeles, California 90033.

Materials and methods

Six months' data were utilized from the prospective continual surveillance of maternal morbidity from the obstetric service at the LAC-USC Medical Center, in the interval from March 1, 1973, to August 31, 1973. This interval was chosen for it represented a period in which infection surveillance was well established and this time span preceded the widespread clinical use of prophylactic antibiotics. A system for obstetric surveillance has been previously described.[2] It included twice-weekly rounds on all postpartum patients in the hospital who had an oral temperature recorded of 100.4° F. or above, as well as a review of all the bacterial cultures obtained by the obstetric service during that time period. For the purposes of this study, any patient reviewed because of an elevated temperature or a positive culture, who had systemic antibiotics prescribed by the clinician for amnionitis or an endomyometritis, was included. Those patients with community-acquired infection, i.e., those who were febrile at the time of admission were excluded. In order to test the accuracy of the prospective surveillance, a retrospective in depth analysis of all the

Table I. Distribution of deliveries

	Cesarean section	*Vaginal*	*Total*
Monitored	223	1,236	1,459
Not monitored	274	3,445	3,719
Elective repeat	21	—	21
Unable to categorize	5	—	5
Community acquired infection	3	33	36
Total	526	4,714	5,240

Table II. Distribution of hospital-acquired infections

	Cesarean section	*Vaginal*	*Total*
Monitored	90	33	123
Not monitored	56	49	105
Elective repeat	1	—	1
Total	147	82	229

Table III. Time interval of monitoring

	No. of observations	*Mean (min.)*	*Median (min.)*	*95% confidence interval (min.)*
A. Vaginal deliveries:				
1. Uninfected	1,159	300	266	20-780
2. Infected	33	363	345	15-960
B. Cesarean sections:				
1. Uninfected	126	432	406	20-1,200
2. Infected	90	519	472	25-1,130

records of patients with the highest risk of infection, i.e., patients who had been monitored and who then had cesarean section, was performed.

All monitored patients had the length of time recorded in minutes by direct analysis of the monitor tracing from the application of the electrode and the introduction of the intrauterine pressure catheter until delivery. All of the patients had the two devices applied simultaneously.

A potent factor in skewing data on the incidence of hospital acquired infection is the prophylactic use of antibiotics. On our obstetric service, this practice has been restricted to a minority of patients undergoing cesarean section. All of the patients who had a cesarean section after monitoring had their hospital records reviewed. There were seven occasions when prophylactic antibiotics were used among the 133 uninfected cesarean section patients who were monitored (5.3 per cent). These were dropped from the statistical analysis.

All patients admitted to the fetal intensive care unit (FICU) of the obstetric service at the LAC-USC Medical Center during this study interval were at high risk for at least one maternal, fetal, or obstetric factor. Of the 1,459 patients admitted to the FICU during the time span of the study, 718 (49.2 per cent) were admitted because of the presence of either ruptured membranes without labor or poor progress in labor as manifested by an abnormal cervical dilatation record. This figure does not include those patients who later required pitocin augmentation but who were admitted to the unit for some other reason.

Results

Distribution of patients. In the 6 months' time interval of this study, there were 5,240 deliveries at the Women's Hospital of the LAC-USC Medical Center (see Table I). In five of the 526 patients undergoing cesarean section, no monitor records were available and we were unable to document the use of internal monitoring. These patients were dropped from consideration. We were able to categorize all of the vaginal deliveries, but 77 of 1,236 monitor records of uninfected cases were not available for analysis. All of the monitor records for infected patients were available for review. The cesarean section rates for monitored and nonmonitored patients were 15.3 and 7.4 per cent. The difference in these rates is statistically significant ($P < 0.002$).

Distribution of infected patients. Table II gives the distribution of the 229 cases of hospital-acquired infections which were observed. The rates of hospital-acquired uterine infection were: cesarean sections, monitored, 90 per 223 (40.4 per cent); cesarean section, not monitored (excluding elective repeat cesarean sections), 56 per 271 (20.4 per cent); elective repeat cesarean sections, 1 per 21 (5 per cent); vaginal deliveries monitored, 33 per 1,235 (2.7 per cent); vaginal deliveries not monitored 49 per 3,445 (1.4 per cent). There is a statistically significant increase in the number of infections in women undergoing cesarean section who are monitored ($P < 0.002$). This same difference occurs following vaginal delivery with $P < 0.005$. The method of analysis used for determination of the P value was a t test by proportions.

Time duration on the monitor. Table III gives the duration of time of internal monitoring in patients categorized by route of delivery and the presence or absence of a hospital-acquired uterine infection. There are a number of reasons for the differences in the numbers of observations in Table I and Table III. Only 1,159 of the 1,236 monitor records from those women delivered vaginally, and not infected, were available for analysis. Seven of the 133 noninfected cesarean section patients were not analyzed for they received prophylactic antibiotics. Fig. 1. depicts the numbers of

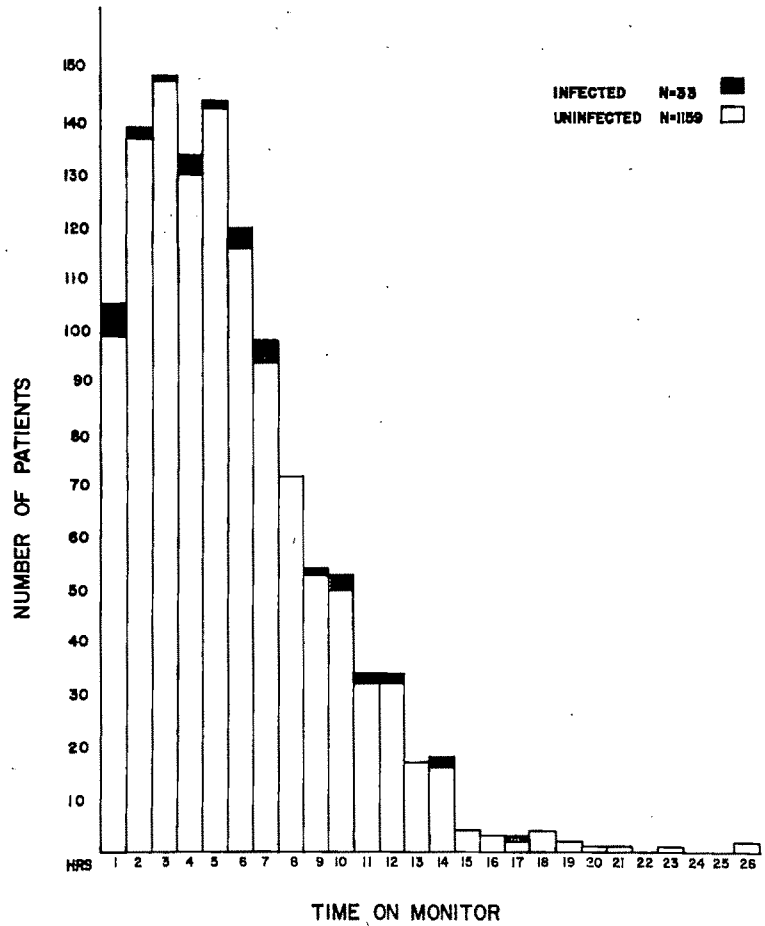


Fig. 1. The length of time of internal monitoring and the number of women with or without infection who delivered vaginally. Each bar represents the total number of women monitored for that time interval. For example, the bar above hour No. 1 represents the total number of women monitored for 1 hour or less, the bar above hour No. 2 represents the total number of women who were monitored for an interval of 1 to 2 hours.

monitored women who delivered vaginally, based upon the time interval. The infected population is compared to the uninfected group. The differences noted are not statistically significant. Fig. 2 shows the numbers of monitored women who were delivered by cesarean section, based again upon time intervals. The infected population is compared to those women free of infection. Again, the differences noted are not statistically significant.

Comment

This study presents an accurate picture of the current hospital-acquired uterine infection rate in a large urban obstetric service. This accuracy was assured by a prospective surveillance survey of microbiologic data and biweekly rounds on the postpartum service. There are shortcomings to any prospective system and ours was no exception. Patients treated with antibiotics during labor for amnionitis, whose cultures were not obtained or lost, and who had no postpartum fever, would not have been detected by such a system. Our survey of the highest risk population revealed an under-reporting of infection of 10 per cent. In addition, the inclusion of patients as infected who receive powerful systemic antibiotics with the first postpartum temperature elevation must add some women who in the past were diagnosed as having 1 day fever. These shortcomings of under- and over-reporting exist in both the monitored and nonmonitored groups. For the purposes of this study, the data provide good insight into the obstetric practices at the LAC-USC Medical Center.

On this huge obstetric service the selection of patients for intrapartum monitoring results in a population at high risk for a postpartum infection. The incidence of a postpartum endomyometritis was significantly

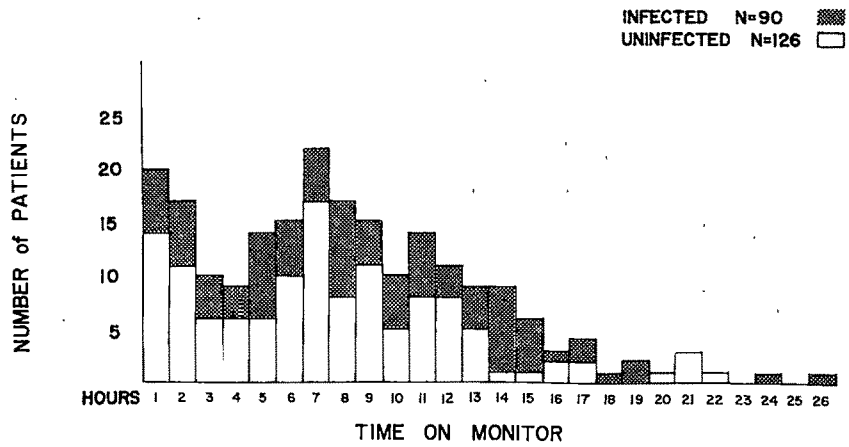


Fig. 2. The length of time of internal monitoring and the number of women with or without infection who delivered by cesarean section. Each bar represents the total number of women monitored for that time interval. For example, the bar above hour No. 1 represents the total number of women monitored for 1 hour or less, the bar above hour No. 2 represents the total number of women who were monitored for an interval of 1 to 2 hours.

greater among monitored women, whether they were delivered vaginally or by cesarean section. These results in patients with an endomyometritis can be compared to a recent evaluation of bacteremia from the same obstetric unit.[3] In that study, a significantly greater number of monitored patients had a postpartum bacteremia, but statistical significance could not be demonstrated when monitored cesarean section patients were compared to nonmonitored cesarean section patients.

Monitoring was not the only factor involved in the development of a postpartum endomyometritis. Cesarean section is followed by a much higher incidence of postpartum soft-tissue pelvic infection than a vaginal delivery. In fact, the risk for a postpartum endomyometritis is significantly greater in nonmonitored patients undergoing cesarean section than in monitored patients delivered vaginally. Monitoring in this institution does identify a high-risk population. This is important to recognize. Any prospective study of preventive measures—for example, prophylactic antibiotics in a cesarean section—could yield a wide difference for equivalent treatments if one group consisted primarily of low-risk nonmonitored patients and the other had a high proportion of monitored patients.

Previous studies of the influence of monitoring upon maternal postpartum morbidity have yielded conflicting results. Chan and associates[4] and Wiechetek and associates[5] could not demonstrate any difference in maternal morbidity, whether or not monitoring was carried out. In contrast, Larsen and associates,[6] in a prospective study from Yale, showed an increase in maternal morbidity following monitoring. Of particular interest was the observation of a significant incidence of maternal morbidity when the duration of monitoring exceeded 8 hours.[6] If this observation could be verified in our large clinical service, it would be an important guide to the therapy of monitored patients.

Although this study establishes a higher incidence of maternal infection among monitored patients, we do not believe a cause-and-effect relationship has been established. This belief is based in part upon an analysis of the patient population chosen for internal monitoring on the obstetric service of the LAC-USC Medical Center. During this 6 month time interval, nearly 50 per cent of the women being monitored had poor progress in labor with ruptured membranes, prior to the use of a monitor. In addition, a higher proportion of the monitored population came to cesarean section, and previous studies have shown the population of women in labor who are delivered by cesarean section is at high risk for infection, whether monitored or not.[7, 8] Although this study does not establish an absence of a relationship between monitoring and infection, this selection of patients seems to be a more critical factor in maternal morbidity than the monitoring itself.

An additional reason for our skepticism about a predominant role of monitoring in maternal infection was our inability to verify the assessment of Larsen and associates[6] of an association of a prolonged interval of monitoring with an increased incidence of infection. Frankly, we were surprised with these results. In comparing the population of monitored women with and without infection by vaginal delivery or cesarean sec-

tion, we could demonstrate no statistical difference between the two groups (see Fig. 1 and 2). This lack of discrimination between the length of time of monitoring between infected and noninfected patients has great clinical significance. Our data suggest that any arbitrary attempt to assign a time limit for a monitoring interval among a high-risk obstetric population to prevent maternal infection is not justified because maternal infection is not an all-or-none phenomenon. For example, fewer than 5 per cent of monitored patients delivered vaginally have any postpartum evidence of infection. Again, our study does not rule out the possibility of some relationship between the time interval of monitoring and maternal infection. The information available from this study indicates that in this high-risk obstetric population, invasive monitoring techniques are not as critical a factor as cesarean section in maternal infections. It could well be that there is a correlation between the length of time of membrane rupture and maternal infectious morbidity. This variable is currently under investigation.

Prospective studies could be planned to assess more exactly the role of internal monitoring in the development of maternal soft-tissue pelvic infections. One study might focus upon a high-risk obstetric population, with these patients randomly assigned to an invasive or noninvasive monitoring category. Another proposed study might randomly assign women not considered at high risk to either an invasive or a noninvasive monitoring category. This is a population with a low incidence of infection and a previous evaluation by Chan and associates[4] demonstrated few infections in this monitored population. Thousands of observations might be needed to demonstrate statistical significance, if indeed it exists.

Statistical significance is really not the important issue with internal monitoring. Instead, the obstetrician wishes to know the clinical significance of this procedure in patients who most need monitoring, i.e., those at high risk. This study answers one important clinical question. The length of time of monitoring is not directly related to maternal infectious morbidity in a high-risk obstetric population. In viewing risk factors, cesarean section, particularly in the woman in labor, must be ranked as a more significant variable in maternal morbidity than monitoring.

REFERENCES

1. Hon, E.: Additional observations on pathologic bradycardia, AM. J. OBSTET. GYNECOL. **118:** 428, 1974.
2. Ledger, W. J., Reite, A. M., and Headington, J. T.: A system for infectious disease surveillance on an obstetric service, Obstet. Gynecol. **37:** 769, 1971.
3. Ledger, W. J., Norman, M., Gee, C. L., and Lewis, W. P.: Bacteremia on an obstetric-gynecologic service, AM. J. OBSTET. GYNECOL. **121:** 205, 1975.
4. Chan, W. H., Paul, R. H., and Toews, J.: Intrapartum fetal monitoring: Maternal and fetal morbidity and perinatal morbidity, Obstet. Gynecol. **41:** 7, 1973.
5. Wiechetek, W. J., Horiguchi, T., and Dillon, T. F.: Puerperal morbidity and internal fetal monitoring, AM. J. OBSTET. GYNECOL. **119:** 230, 1974.
6. Larsen, J. W., Goldkrand, J. W., Hanson, T. M., and Miller, C. R.: Intrauterine infection on an obstetric service, Obstet. Gynecol. **43:** 838, 1974.
7. Benaron, H. B., and Tucker, B. E.: The effect of obstetric management and factors beyond clinical control on maternal mortality rates at the Chicago Maternity Center from 1959 to 1963, AM. J. OBSTET. GYNECOL. **110:** 1113, 1971.
8. Sweet, R. L., and Ledger, W. J.: Puerperal infectious morbidity, AM. J. OBSTET. GYNECOL. **117:** 1093, 1973.

Renal clearances of estriol conjugates in normal human pregnancy at term

BRUCE K. YOUNG, M.D.*
HELMUT JIRKU, PH.D.
SUSAN KADNER, B.S.
MORTIMER LEVITZ, PH.D.
New York, New York

In late human pregnancy more than 90 per cent of the total estriol (E_3) in body fluids consists of four conjugates, estriol-3-sulfate (E_3-3S), estriol-16-glucosiduronate (E_3-16G), estriol-3-glucuronide (E_3-3G), and estriol-3-sulfate-16-glucosiduronate (E_3-3S-16G). Since the relative amounts of E_3 in blood and urine would be determined by the kidney, the renal clearance of each conjugate was determined and compared with inulin and p-aminohippuric acid (PAH) clearance, as measures of glomerular filtration rate (GFR) and the effective renal plasma flow. Five women were studied in the lateral decubitus position with inulin and PAH infusion. Samples of blood and urine were collected at 40 minute intervals and analyzed. The method for E_3 conjugates involved separation of the four conjugates on Sephadex LH-20, enzyme hydrolysis, and radioimmunoassay. Renal clearances for E_3-3S and E_3-3S-16G were below inulin. E_3-3G approximated inulin; E_3-16G exceeded inulin and approached PAH. In plasma E_3-3S-16G represented 48.4 ± 7.2 per cent; in urine E_3-16G represented 69.5 ± 7.3 per cent of total E_3. Thus, different conjugates predominate in blood and urine.

IN LATE HUMAN pregnancy estriol is synthesized mainly in the placenta from 16α-hydroxy-dehydroepiandrosterone sulfate, principally of fetal origin.[1, 2] An additional source of estriol is by conversion from estrone in the maternal and fetal livers.[3] The estriol so produced is metabolized almost exclusively to conjugates which are excreted in the urine.[4] Since four principal conjugates are involved; estriol-3-sulfate (E_3-3S), estriol-16-glucosiduronate (E_3-16G), estriol-3-glucuronide (E_3-3G), and estriol-3-sulfate-16-glucosiduronate (E_3-3S-16G), the relative amounts of estriol in the urine and blood would be controlled to a large degree by the renal clearance of each of these conjugates. Since estriol levels in these fluids are accepted indicators of fetal-placental health,[5, 6] a study was undertaken to measure the renal clearances of each estriol conjugate in normal pregnancy at term. In four of the five studies comparisons were made with the clearances of inulin and p-aminohippuric acid (PAH) which reflect, respectively, the glomerular filtration rate (GFR), and the effective renal plasma flow.[7]

From the Department of Obstetrics and Gynecology, New York University School of Medicine.

Supported by a grant from the National Institute of Health (Grant CA 02071).

Part of this study was presented at the Fourth International Congress on Hormonal Steroids, Mexico City, Mexico, September, 1974.

Received for publication October 7, 1975.

Accepted October 30, 1975.

Reprint requests: Mortimer Levitz, Ph.D., Department of Obstetrics and Gynecology, New York University Medical Center, 550 First Ave., New York, New York, 10016.

**Irma T. Hirschl Career Scientist.*

Materials and methods

Materials. The four radioactive estriol conjugates used were synthesized in this laboratory from 2,4,6,7-^{3}H-estriol (New England Nuclear Co., Boston, Massachusetts) by published methods. Each conjugate was purified by gradient elution chromatography on Celite as described.[8]

Analytical methods. The procedure for the analysis of estriol conjugates in plasma and urine is similar to that described in detail for the analysis of amniotic fluid.[9] Briefly, about 2,000 c.p.m. of each tritiated estriol conjugate are added to 0.2 to 0.5 ml. of urine or plasma. These serve both as markers for the endogenous conjugates and as tracers for the correction of methodological losses. After precipitation of the pro-

Table I. Concentration of estriol conjugates in plasma (P) and urine (U) in three successive 40 minute periods in Patient M

	E_3-3S*		E_3-16G		E_3-3G		E_3-3S-16G		Total (μg/ml.)
	μg/ml.	%†	μg/ml.	%	μg/ml.	%	μg/ml.	%	
P-0	0.017	14.5	0.018	15.4	0.028	23.8	0.054	46.2	0.117
P-1	0.016	13.6	0.017	14.4	0.025	21.2	0.060	50.8	0.118
P-2	0.017	13.9	0.024	19.7	0.016	13.1	0.065	53.3	0.122
P-3	na‡		0.023		0.014		0.074		
U-1	0.33	7.0	3.05	65.7	0.65	14.0	0.62	13.3	4.64
U-2	0.84	8.8	5.79	61.2	1.35	14.2	1.49	15.8	9.46
U-3	0.44	7.7	3.72	65.1	0.70	12.2	0.86	15.0	5.70

*Abbreviations of estrogen conjugates indicated in text.
†Indicates % contribution of the conjugate to the calculated total.
‡Not analyzed—sample lost.

Table II. Concentration of estriol conjugates in plasma (P) and urine (U) in three successive 40 minute periods in patient A*

	E_3-3S		E_3-16G		E_3-3G		E_3-3S-16G		Total (μg/ml.)
	μg/ml.	%	μg/ml.	%	μg/ml.	%	μg/ml.	%	
P-0	0.020	12.3	0.052	31.9	0.028	17.2	0.063	38.6	0.163
P-1	0.021	12.4	0.043	25.3	0.032	18.8	0.074	43.5	0.170
P-2	0.017	13.9	0.036	29.5	0.016	13.1	0.053	43.5	0.122
P-3	0.024	12.5	0.056	29.2	0.033	17.2	0.079	41.1	0.192
U-1	0.32	2.4	9.85	76.2	1.83	14.1	0.94	7.3	12.94
U-2	0.45	2.8	11.18	71.0	2.88	18.3	1.24	7.9	15.75
U-3	0.47	3.0	11.85	75.6	2.18	13.9	1.18	7.5	15.68

*Footnotes to Table I also apply here.

teins with ethanol, the conjugates are converted to their triethylammonium salts and separated on a Sephadex LH-20 column. Each conjugate is hydrolyzed with Glusulase and the estriol is purified by solvent partitions. The estriol is submitted to radioimmunoassay using rabbit antisera (kindly supplied by Dr. Uwe Goebelsmann) highly specific toward estriol.[10]

Subjects. Five women volunteered for the study. Each patient was about to undergo repeat cesarean section at 39 weeks' gestation and there were no clinical or laboratory abnormalities. A Foley catheter was inserted for the collection of urine and an intravenous infusion was started. The patient received a priming dose of 8 mg. per kilogram of PAH and 50 mg. per kilogram of inulin in normal saline. This was followed by a continuous drip of 500 ml. of normal saline containing 12.5 Gm. of mannitol, 8 Gm. of inulin, and 3 Gm. of PAH, at 2 ml. per minute. The patient remained on her left side as much as possible during the procedure. Blood samples were drawn at time zero and then at three 40 minute intervals, during which time three urine samples were collected. The bladder was emptied with suprapubic pressure. The plasma was separated promptly and stored together with the urine samples at −17° C. until processed. Aliquots were analyzed for PAH and inulin.[7]

The renal clearances (RC) of PAH, inulin, and each estriol conjugate were calculated according to the formula: RC = UV/P, where U and P refer to the concentrations in the urine and plasma, respectively, and V is the urinary output in milliliters per minute. The value for P is the average of the concentrations at the beginning and the end of the test period. All clearances were corrected for surface area using the standard nomogram based on height and weight.

Results

The concentrations of estriol conjugates in each plasma and urine sample collected from the five patients are shown in Tables I to V. The tables also include the per cent contribution of each conjugate to the calculated total. The following features are worthy of comment. (1) E_3-16G and E_3-3S-16G comprised about 80 per cent of the total conjugated estriol in both fluids, but E_3-3S-16G predominated in the plasma whereas E_3-16G was more concentrated in the urine. (2) The per cent contribution of E_3-3G to plasma is similar to that in urine. (3) The per cent contribution of each conjugate to the total is far more stable in the urine than in the plasma. (4) In Patients M and E, the calculated total plasma estriol is remarkably stable but in the other three cases the differences between the

Table III. Concentration of estriol conjugates in plasma (P) and urine (U) in three successive 40 minute periods in Patient E*

	E_3-3S		E_3-16G		E_3-3G		E_3-3S-16G		Total
	μg/ml.	%	μg/ml.	%	μg/ml.	%	μg/ml.	%	(μg/ml.)
P-0	0.044	19.9	0.063	28.5	0.029	13.1	0.085	38.5	0.221
P-1	0.037	19.4	0.063	33.0	0.026	13.6	0.065	34.0	0.191
P-3	0.045	22.0	0.055	27.0	0.028	13.7	0.076	37.3	0.204
U-1	0.92	3.7	20.1	80.5	2.29	9.2	1.64	6.6	24.9
U-2 + 3†	0.66	2.7	20.6	83.5	2.19	8.9	1.20	4.9	24.6

*See Table I footnotes for pertinent explanations.
†Sample P-2 was lost, consequently urines 2 and 3 were combined.

Table IV. Concentration of estriol conjugates in plasma (P) and urine (U) in three successive 40 minute periods in Patient C*

	E_3-3S		E_3-16G		E_3-3G		E_3-3S-16G		Total
	μg/ml.	%	μg/ml.	%	μg/ml.	%	μg/ml.	%	(μg/ml.)
P-0	0.060	18.0	0.052	15.7	0.047	14.2	0.173	52.1	0.332
P-1	0.048	18.6	0.065	25.2	0.016	6.2	0.129	50.0	0.258
P-2	0.066	23.7	0.049	17.6	0.034	12.2	0.129	46.4	0.278
P-3	0.054	20.6	0.061	23.3	0.025	9.5	0.122	46.6	0.262
U-1	1.58	2.8	45.1	79.5	3.36	5.9	6.37	11.8	56.8
U-2	1.36	3.2	33.7	79.9	2.50	5.9	4.60	10.9	42.2
U-3	0.92	2.6	27.9	79.3	2.29	6.5	4.09	11.6	35.2

*Footnotes to Table I also apply here.

extremes are from 18 per cent to 30 per cent.

Table VI shows the calculated renal clearances of each conjugate. In four patients the renal clearances of PAH and inulin were also determined and the data are presented in the same table. In general, the renal clearance of E_3-16G far exceeded that of E_3-3G and was about 10 times that of E_3-3S or E_3-3S-16G, which were similar. In Patients A and C the renal clearances of E_3-16G were similar to that of PAH, whereas in the other subjects they were lower. Nevertheless, the values clearly exceeded those for inulin clearance. Generally, the RC of E_3-3G was comparable to that of inulin. The RC of E_3-3S or E_3-3S-16G was significantly lower than the value for inulin.

Comment

There are reports on the assay of estriol conjugates in plasma and urine in human pregnancy. Investigating plasma Goebelsmann and associates[11] separated the four conjugates by countercurrent distribution and quantitated the estriol fluorometrically. Tikkanen[12] combined separation on Sephadex with gas-liquid chromatography for the estimation of estriol conjugates in urine. Our method is the simplest reported, in that the conjugates are separated clearly on a single short Sephadex LH-20 column. Furthermore, only 0.5 ml. of fluid is required for analysis. A comparison between the average values obtained in our studies and those reported by these investigators are presented in Table VII.

This is the first study which focuses in detail on the concentrations of estriol conjugates in the urine and plasma in a way that permits the estimation of renal clearance rates of each conjugate. Studies on clearance are influenced by the fact that renal function of women in late pregnancy is altered by position. Measurements of GFR based on inulin clearance and renal blood flow, based on PAH clearance, show a 20 per cent decrease when the patient is supine, compared with measurements in the lateral decubitus position.[13] Accordingly, the subjects were asked to maintain the lateral position throughout the experiment. There is another potential source of error in these determinations. The urine collections were virtually complete, so an aliquot represents the average excretion for that collection period. However, there were some rather wide changes in the plasma concentrations of estriol conjugates. Averaging values in the plasma at the start and end of the 40 minute period does not necessarily produce the mean for that period. In clearance studies multiple observations made on each subject usually compensates for this deficiency in such a difficult experimental protocol. In this connection it should be noted that undefined factors involving moment to moment biologic changes in mother and fetus may produce rapid alterations in the concentration of estriol conju-

Table V. Concentration of estriol conjugates in plasma (P) and urine (U) in three successive 40 minute periods in Patient G*

	E_3-3S		E_3-16G		E_3-3G		E_3-3S-16G		Total
	μg/ml.	%	μg/ml.	%	μg/ml.	%	μg/ml.	%	(μg/ml.)
P-0	0.032	12.4	0.069	26.8	0.058	22.6	0.098	38.2	0.257
P-1	0.035	14.9	0.068	29.1	0.046	19.7	0.085	36.3	0.234
P-2	0.035	17.9	0.045	23.0	0.036	18.4	0.080	40.7	0.196
P-3	0.026	13.1	0.022	11.1	0.023	11.6	0.128	64.2	0.199
U-1	0.217	3.6	3.93	65.8	1.31	22.0	0.514	8.6	5.98
U-2	0.282	4.1	4.51	66.2	1.55	22.7	0.476	7.0	6.81
U-3	0.211	3.6	4.09	69.5	1.13	19.2	0.455	7.7	5.88

*Footnotes to Table I also apply here.

Table VI. Renal clearances* of estriol conjugates, p-aminohippuric acid (PAH), and inulin in late human pregnancy

			Renal clearance					
			Estriol conjugate†					
Patient	Time period‡	Urine output (ml./min.)	E_3-3S	E_3-16G	E_3-3G	E_3-3S-16G	PAH	Inulin
M	1	1.2	23	201	274	12	483	74
	2	1.6	76	409	96	35	874	136
	3	2.8	—	405	119	31	736	128
Average			50	338	163	26	698	113
A	1	2.0	32	436	129	29	351	89
	2	1.2	29	352	149	25	346	60
	3	1.4	35	383	133	27	356	56
Average			32	390	137	27	351	68
E	1	2.5	67	940	245	65	1369	99
	2 + 3	1.88	35	447	181	38	1440	74
Average			51	694	213	52	1405	87
C	1	0.7	19	508	70	29	637	107
	2	0.6	14	343	58	21	364	80
	3	0.9	13	428	65	27	282	71
Average			15	426	64	26	428	86
G	1	1.1	7	61	27	6	—	—
	2	2.5	19	194	91	14	—	—
	3	3.1	20	361	113	13	—	—
Average			15	205	77	11		

*Values are in ml. per minute.

†Abbreviations of estriol conjugates in text.

‡Successive 40 minute collections except in Patient E, where 2 + 3 is for 80 minutes.

gates in the blood. Similar changes may be masked by analyzing an aliquot from urine collected over a given time period. Consequently, we are presently unable to interpret the significance of the observation that the per cent contribution of each conjugate to the total varied in the plasma samples, but remained quite constant in the urines. Another variable meriting consideration is the possible change in renal function with gestation. Accordingly, it is emphasized that the data accumulated in this study pertain to subjects at term.

Renal handling of the different estriol conjugates showed differences related to the presence of a sulfate moiety and to the site of glucuronidation. E_3-3S-16G and E_3-3S (except in Subject M) were far more concentrated in the plasma, whereas E_3-16G predominated in the urine. E_3-3G contributed to both fluids about equally. Consistent with these data is the observation that the calculated renal clearances of E_3-16G and E_3-3G clearly exceed those of E_3-3S and E_3-3S-16G. These differences may be explained partly in terms of the relative binding to serum proteins. Goebelsmann and associates[11] studied the binding of each estriol conjugate to serum using the methods of equilibrium dialysis and gel filtration on Sephadex G-25 columns. By each method the binding of E_3-3S and E_3-3S-16G was nearly 90 per cent, about twice that of E_3-16G or E_3-3G. The avidity of binding of the

Table VII. Estriol conjugates in plasma and urine in late human pregnancy

	Urine		*Plasma*	
*Conjugates**	*Reported*[12]	*This study*†	*Reported*[11]	*This study*†
E_3-3S	2.5	5.1 ± 2.3	30.1	16.2 ± 5.2
E_3-16G	68.0	69.5 ± 7.3	17.7	24.2 ± 2.8
E_3-3G	22.9	13.0 ± 4.3	11.8	11.2 ± 2.3
E_3-3S-16G	6.5	12.4 ± 2.3	40.8	48.4 ± 7.2

Values are in per cent of total estriol conjugates in the fluid indicated. They are calculated from the concentrations.

*Abbreviations of estriol conjugates in text.

†The figures are the averages of the values from the five subjects studied. The average deviations are also shown.

sulfate esters of E_3 to plasma proteins would reduce the GFR and probably tubular secretion, since it is postulated that the unbound conjugate is very likely the specie cleared. Based on these marked differences in binding to plasma proteins, the clearance rates of the simple glucosiduronates would be about 5 times greater than the sulfates. However, in the absence of information on the relative rates of release from binding such estimates are speculative.

An interesting observation is that the calculated renal clearance of E_3-16G approaches that of PAH and exceeds that of E_3-3G. Apparently tubular secretion is a more important route for the disposition of E_3-16G. However, a complicating feature is that the kidney can convert E_3 to E_3-16G.[14] Although the concentrations of unconjugated E_3 in the plasma are quite low, renal conversion to E_3-16G introduces an error in the estimated renal clearance of E_3-16G of unknown magnitude. There is no present evidence that the kidney is involved in the metabolism of the other 3 conjugates or that tubular reabsorption plays a role.

These patterns indicate that measurements of blood estriol and urinary estriol are in effect, looking at different species of estriol. Since the usual assays are of total E_3, the fact that different conjugates predominate in various body fluids has not received adequate consideration. Complications of pregnancy such as preeclampsia and diabetes affect renal function. Furthermore, medical complications such as obstructive jaundice have been shown to alter the urinary excretion of E_3-3G, presumably the result of decreased production of this conjugate.[15] Further study of E_3 conjugates in abnormal pregnancies may reveal other specific differences in E_3 metabolism, as well as explain discrepancies between blood and urine estriol concentrations such as those observed in some cases of class D diabetes mellitus.[16]

The authors are grateful to Drs. David Baldwin and Jerome Lowenstein for valuable discussions and advice, and also to Dr. Marilyn Cozzens-Kessler for the determinations of p-aminohippuric acid and inulin.

REFERENCES

1. Ryan, K. J.: Metabolism of C-16-oxygenated steroids by human placenta: The formation of estriol, J. Biol. Chem. **234:** 2006, 1959.
2. Siiteri, P. K., and MacDonald, P. C.: Placental estrogen biosynthesis during human pregnancy, J. Clin. Endocrinol. **26:** 751, 1966.
3. Schwers, J., Eriksson, G., and Diczfalusy, E.: Metabolism of oestrone and oestradiol in the human foeto-placental unit at mid-pregnancy; Acta Endocrinol. (Kbh.) **49:** 65, 1965.
4. Levitz, M., and Katz, J.: The synthesis and some properties of estriol-15-^{3}H, Steroids **5:** 11, 1965.
5. Nachtigall, L. M., Bassett, M., Hogsander, U., and Levitz, M.: Plasma estriol levels in normal and abnormal pregnancies: An index of fetal welfare: AM. J. OBSTET. GYNECOL. **101:** 638, 1968.
6. Greene, J. W., Jr., Smith, K., Kyle, G. C., Touchstone, J. C., and Duhring, J. L.: The use of urinary estriol excretion in the management of pregnancies complicated by diabetes mellitus, AM. J. OBSTET. GYNECOL. **91:** 684, 1965.
7. Smith, H. W.: Principles of Renal Physiology, New York, 1956, Oxford University Press, Inc.
8. Young, B. K., Jirku, H., and Levitz, M.: Estriol conjugates in amniotic fluid at midpregnancy and term, J. Clin. Endocrinol. **35:** 208, 1972.
9. Young, B. K., Jirku, H., Slyper, A. J., Levitz, M., Kelly, W. G., and Yaverbaum, S.: Estriol conjugates in amniotic fluid of normal and Rh-isoimmunized patients, J. Clin. Endocrinol. **39:** 842, 1974.
10. Katagiri, H., Stanczyk, F. Z., and Goebelsmann, U.: Estriol in pregnancy. III. Development, comparison and use of specific antisera for rapid radioimmunoassay of unconjugated estriol in pregnancy plasma, Steroids **24:** 225, 1974.
11. Goebelsmann, U., Chen, L.-C., Saga, M., Nakamura, R. M., and Jaffe, R. B.: Plasma concentration and protein binding of oestriol and its conjugates in pregnancy, Acta Endocrinol. (Kbh.) **74:** 592, 1973.
12. Tikkanen, M. J.: Urinary excretion of estriol conjugates in normal pregnancy, J. Steroid Biochem. **4:** 57, 1973.
13. Chesley, L. C. and Sloan, D. M.: The effect of posture on renal function in late pregnancy, AM. J. OBSTET. GYNECOL. **89:** 754, 1964.
14. Kirdani, R. Y., Sampson, D., Murphy, G. P., and Sandberg, A. A.: Studies on phenolic steroids in human subjects. XVI. Role of the kidney in the disposition of estriol, J. Clin. Endocrinol. **34:** 546, 1972.
15. Adlercreutz, H., and Tikkanen, M. J.: Defects in hepatic uptake and transport and biliary excretion of estrogens: Some new concepts of liver metabolism, Med. Chir. Di. **2:** 59, 1973.
16. Levitz, M., and Selinger, M.: Plasma estriol levels in class D diabetes of pregnancy, AM. J. OBSTET. GYNECOL. **108:** 82, 1970.

Neonatal respiratory distress following elective delivery. A preventable disease?

MAUREEN HACK, M.B.CH.B.
AVROY A. FANAROFF, M.B., M.R.C.P.E.
MARSHALL H. KLAUS, M.D.
BARRY D. MENDELAWITZ, M.B., M.R.C.O.G.
IRWIN R. MERKATZ, M.D.
Cleveland, Ohio

Twelve per cent of all infants with respiratory distress admitted to our neonatal intensive-care unit from November, 1973 to April, 1974, were born after elective intervention (15 cesarean sections and four vaginal inductions). All were white and 18/19 were private compared to yearly admissions of white (56 per cent) and private (57 per cent). Eighteen of 19 were admitted from the region via the transport service. Mean birth weight was 2.69 kilograms, with 18 infants over 2 kilograms. Pediatric gestational age from a physical and neurological evaluation ranged from 32 to 39 weeks (mean 36.2 weeks) in contrast to obstetric dating which ranged from 38 to 44 weeks (mean 39 weeks). The obstetric dating was 3 or more weeks greater than the pediatric age in 11 infants. Pulmonary disease included transient tachypnea (5) and respiratory distress syndrome (14). No prior documentation of pulmonary maturity had been obtained in any of these infants. Mean hospitalization was 23 days (range 1 to 140), with estimated costs of $3,421 per baby. Two infants died. Respiratory distress following elective delivery remains a potent source of on-going perinatal morbidity. Regional programs must direct increased educational efforts to eliminate this preventable disease.

THIS REPORT describes the continuing "toll" of potentially preventable morbidity in infants delivered electively who subsequently require emergency transport to and treatment at a Perinatal Center. Typically the affected infants have been white, private patients, weighing over 2,000 grams, and most have developed severe respiratory disease.

The reliability of ultrasonography and amniotic fluid assays for diagnosis of fetal age and pulmonary maturity is now generally accepted.[1-3] These tests are routine in the management of high-risk pregnancies. Our data will emphasize the need for continuing education, wider availability, and a more systematic application of these procedures on a regionalized basis especially prior to any elective intervention.

From the Neonatal Intensive Care Unit and Perinatal Center, Departments of Pediatrics and Reproductive Biology, Case Western Reserve University, School of Medicine.

Supported in part by the Educational Foundation of America.

Received for publication July 25, 1975.

Revised December 22, 1975.

Accepted January 6, 1976.

Reprint requests: Dr. Merkatz, University Hospital of Cleveland, MacDonald House, 2105 Adelbert Rd., Cleveland, Ohio 44106.

Material and methods

The Neonatal Intensive-Care Unit (N.I.C.U.) at Rainbow Babies and Childrens Hospital, Cleveland, admits infants from the adjoining obstetric unit and 27 hospitals of Greater Cleveland. The referral area has approximately 24,000 deliveries per year.

All admissions to the N.I.C.U. were prospectively analyzed for a 6 month period from October 1, 1973, to March 31, 1974. During this time 245 infants were admitted, of whom 19 (8 per cent) were born after *elective* intervention (15 cesarean sections and four vaginal inductions). All of these babies had significant respiratory problems and accounted for 12 per cent of the 158 infants with respiratory distress seen during this interval. They were transferred from 10 different hospitals and included one infant delivered at our

Table I. Clinical details of babies delivered electively

Case No.	Gestational age (wk.) Ob†	Ped‡	Weight (Gms.)	Apgar 1 min.	5 min.	Neonatal morbidity	Hospital days	Cost* ($)	Outcome
A. Cesarean section:									
1	39	36	2,100	8	9	Severe RDS,§ CPAP‖	15	3,390	Good
2	40	36	2,900	9	?	RDS, CPAP	11	2,550	Good
3	38	38	3,120	6	7	Transient tachypnea	4	830	Good
4	38	37	3,350	6	8	Severe RDS, CPAP ambient O_2 100% for 72 hr., hypocalcemia (Ca 6.8 mg. per 100 ml.); jaundice (12 mg. per 100 ml. bilirubin)	12	2,800	Good
5	38	37	3,118	7	9	Moderate RDS; pneumothorax	8	1,800	Good
6	39	35	2,020	8	10	Severe RDS, CPAP; pneumothorax; ambient O_2 70% for 84 hr	15	3,387	Adreno-genital syndrome
7	39	35	2,350	Mild asphyxia		Mild RDS	10	2,180	Good
8	38	37	2,500	Asphyxia		Severe RDS, CPAP	11	2,590	Mild retinal vascularization
9	39	35	2,490	7	8	Transient tachypnea	16	3,412	Good
10	39	39	2,740	Asphyxia		Asphyxia neonatorum; transient tachypnea	6	1,312	Good
11	38	32	1,500	Good		Severe RDS, respirator; bilateral pneumothorax; bronchopulmonary dysplasia	140	33,000	Death due to respiratory failure
12	39	38	3,480	8	10	Transient tachypnea; apneic attacks	16	3,390	Good
13	38	36	2,608	7	8	Severe RDS, respirator; shock; disseminated intravascular coagulation; pneumopericardium, thrombotic complications of leg	43	9,140	Good
14	38	34	2,450	Mild asphyxia		Severe RDS, respirator; pneumothorax, jaundice (bilirubin—13 mg. per 100 ml.); hypocalcemia (Ca 5.3 mg. per 100 ml.)	45	9,500	Good
15	40	35	2,325	Good		Severe RDS, CPAP	19	4,277	Good
B. Vaginal induction:									
16	40	36	2,630	9	9	Transient tachypnea	4	855	Good
17	38	38	3,250	5	9	Severe RDS, CPAP	21	2,750	Good
18	44	36	2,960	4	6	Severe RDS, pulmonary hemorrhage; Gr. B. hemolytic streptococcal septicemia	1	346	Death
19	38	35	3,200	Unknown		Severe RDS; respirator	23	5,080	Good

*For calculation of cost estimate, see text.
†Calculated from LMP.
‡Postnatal clinical evaluation.
§Respiratory distress syndrome.
‖Continuous positive airway pressure.

obstetric unit. Pulmonary maturity had not been assessed by amniocentesis prior to the delivery of any of these infants. During the period of observation there were no admissions for respiratory distress occurring after elective deliveries when amniocentesis had revealed mature pulmonary indices.[2, 3]

The weight, race, and social status of all infants admitted to the unit during this period were analyzed. Detailed study for each of the 19 babies born after elective intervention included an analysis of the extenuating indications for delivery, type of anesthesia employed, condition at birth, gestational aging, neonatal morbidity, days of hospitalization, cost estimates, and outcome.

The following definitions were employed:

1. Gestational age. The "obstetric gestational age" is defined as completed weeks from the first day of the last menstrual period. The "pediatric gestational age" is determined by physical characteristics of the infant on admission to the nursery,[4] and by a neurological examination of maturity[5] performed as soon as the condition of the infant permits.

2. Respiratory distress syndrome (RDS) or transient tachypnea of the newborn.

a. Respiratory distress syndrome (RDS). This is diagnosed on the basis of clinical signs, biochemical parameters, and a chest x-ray showing characteristic reticulogranular patterns and air bronchograms. In mild RDS,

the infants do not require an environmental oxygen of more than 70 per cent. In severe RDS, the infants require greater than 70 per cent oxygen and some form of assisted ventilation. In our unit, nasal continuous positive airway pressure (CPAP) is instituted when the arterial oxygen tension is less than 60 mm. Hg with an inspiratory 0_2 of 70 per cent or greater. Mechanical ventilation is commenced if the arterial oxygen tension drops below 40 mm. Hg in 100 per cent oxygen, if there are apneic attacks, or increasing acidosis.

b. Transient tachypnea of the newborn. Diagnosed in infants with persistent tachypnea (respiratory rate above 60 per minute), mild grunting, retractions, and duskiness in room air. Chest x-ray is normal or has perihilar streaking. The oxygen requirements seldom exceed 40 per cent and the condition usually improves within 24 hours.

3. Cost estimates. These are calculated on the basis of: (a) transport by ambulance (average $50.00); (b) hospitalization ($200.00 daily); (c) medical fees ($50.00 for the first day of intensive care, decreasing thereafter to $10.00 per day for routine hospital care); (d) additional charges for special procedures such as exchange transfusions, chest tubes, or respirator care.

Results

1. Birth weights. Of the 158 infants with respiratory distress, 85 weighed over 2,000 grams and 18 (21.2 per cent) of these followed elective delivery. In the elective delivery group, the mean birth weight was 2,690 grams (range 1,500 to 3,480 grams). Eight infants weighed less than 2,501 grams but only one weighed less than 2,001 grams. All birth weights were considered to be appropriate to the postnatal pediatric assessment of gestational age.[6] Diabetes had not been present or detected in any of the mothers.

2. Race and social status. During the study period, 66 per cent of admissions were white whereas all 19 electively delivered babies were white. Eighteen of these 19 were private patients in contrast to an over-all 57 per cent private admission rate.

Analysis of the electively delivered group. Detailed clinical data on the 19 infants and their mothers are summarized in Table I.

Of the 15 cesarean sections, 13 were repeat procedures and two were elective primary sections. The indications for the latter were a prelabor primigravida breech (Baby 1) and a suspected large infant in a patient with a prior child afflicted with cerebral palsy (Baby 2). The extenuating indications for induction of labor in the four patients delivered vaginally included suspected postmaturity (1), urinary tract infection (1), anticipated termination of health insurance (1), and residential distance from the hospital (1).

Table II. Difference between obstetric and pediatric estimation of gestational age

No. of weeks	*No. of infants*
< 2	8
3—4	8
5—6	2
7—8	1
Total	19

General anesthesia was employed for three cesarean sections and spinal anesthesia was used for 12. Three of the vaginal deliveries were conducted under spinal anesthesia and the other two without any anesthesia. Four of the babies were depressed at birth, requiring immediate resuscitation.

The mean obstetric gestational age was 39 weeks (range 38 to 44 weeks); the mean pediatric gestational age was 36.2 weeks (range 32 to 38 weeks). In eight of the 19 infants, the obstetric age was within 2 weeks of the pediatric gestational age. With the other 11 infants, the obstetric gestational age was 3 to 8 weeks greater. (Table II). From a review of the maternal records it was apparent that the antenatal evaluation of fetal maturity was based entirely on clinical criteria and that in no case did the obstetrician benefit from special diagnostic procedures to evaluate fetal age or pulmonary maturity prior to delivery.

The pulmonary disease encountered included severe RDS in 12 infants, mild RDS in two, and transient tachypnea in five infants. Pneumothorax complicated the respiratory distress syndrome and its therapy in five of the patients. One infant (Case No. 13) was admitted with severe RDS, shock, and evidence of disseminated intravascular coagulopathy. Subsequent morbidity included a pneumopericardium and an arterial thrombotic complication.

Two babies died. One infant had severe RDS complicated by bronchopulmonary dysplasia, cor pulmonale, and retrolental fibroplasia. She required respirator care until her death. The other infant was delivered vaginally after elective induction for suspected postmaturity, with an obstetric gestational age of 44 weeks. The pediatric gestational age was 36 weeks. The infant was mildly asphyxiated at birth and developed severe RDS terminating with a massive pulmonary hemorrhage at age 24 hours. Beta-hemolytic streptococcus was cultured from the blood and no doubt contributed to the fulminant course.

The surviving infants were discharged in good condition. One infant (Case No. 8) was followed for mild retrolental fibroplasia which was subsequently resolved.

The duration of hospitalization ranged from 1 to 140 days (mean 23 days). A conservative estimate of

all medical costs yielded an average of $4,978 per baby although the figure is lower ($3,421) if Case No. 11 is excluded because of her prolonged hospitalization.

Comment

The risk of "prematurity" and respiratory problems following elective induction of labor and elective repeat cesarean section has been well documented.[7–10] The associated neonatal morbidity and deaths have been repeatedly emphasized. Despite the preferred alternative of awaiting the onset of labor, there remains a place in obstetric practice for elective deliveries. There are definite advantages to the patient, physician, and hospital staff in selected circumstances. However, these procedures cannot be endorsed if they persist in producing the number and severity of neonatal complications described herein. This is particularly true in light of current evidence that the application of ultrasonography[1] and amniotic fluid indices of maturity[2] can virtually abolish the potential ambiguity in the timing of such deliveries.

The results of this study show that despite the assumed availability of such diagnostic tests for fetal age and functional maturity, they are not being uniformly employed. The consequent "iatrogenic" prematurity and its sequelae continue to contribute a significant proportion of the neonatal disease in our center and presumably in other nurseries throughout the country. The full magnitude of the problem will become evident only after careful evaluation of regional perinatal studies.

In the absence of asphyxia, the incidence of RDS is directly related to the gestational age of the infant, reflecting progressive pulmonary maturity. It is generally considered that beyond 38 weeks' gestation the incidence of RDS is minimal, and it is for this reason that most elective deliveries are scheduled after this point in pregnancy. However, there is recent evidence that the development of pulmonary maturity can be delayed or accelerated in some babies as, for example, in diabetic pregnancies.[3]

Obstetric dating is known to be subject to error, particularly if conception occurs after oral contraceptive therapy or in the setting of irregular menses. Early confirmation of pregnancy under these circumstances is most helpful but still not precise.

Delivery by cesarean section adds an additional risk factor for the development of respiratory distress. A 14-fold increased incidence has been reported, even at 37 to 38 weeks' gestation.[11] Significantly, analysis of the British Perinatal Mortality Data[12] revealed that the incidence of RDS in infants delivered by cesarean section before the onset of labor was four times greater than after labor had commenced.

A review of our data indicates that all 19 elective deliveries were appropriately scheduled after the thirty-eighth week of gestation by obstetric dating. Nevertheless, in 11 of the 19 infants, a discrepancy of more than two weeks was found between the obstetric and pediatric aging.

The techniques employed for pediatric dating included both physical examination and neurological evaluation. The reliability of these two approaches in the newborn period has been assessed by several investigators. Farr and co-workers[13] used the physical characteristics and found a 95 per cent confidence limit within two weeks. Coutts[14] established the validity of the neurological evaluation and Dubowitz and coworkers,[15] using a scoring system which combined both methods, confirmed their findings. It can be reasonably deduced that the discrepancy found in the gestational ages of our babies was valid despite the fact that their mean birth weight was above 2,500 grams.

Significantly, in eight of the 19 infants there was basic agreement (within 2 weeks) between the obstetric and pediatric ages and each of these babies weighed over 2,500 grams. In spite of this fact, seven of these infants developed substantial morbidity. This group clearly illustrates the potential risk of assuming functional maturation even if the dates are accurate. The independent roles of cesarean section and asphyxia may well have been operative in these instances, but without proper documentation there is no way to exclude the presence of delayed pulmonary maturation.

It can be concluded that if this potent cause of perinatal loss and illness is to be avoided, reliable confirmation of functional maturity must be obtained prior to elective intervention. The technology is now available. Although exceptions to a concept of routine amniocentesis or ultrasonography may be reasonable, they should be rare particularly with elective repeat cesarean sections.

The cost of these untoward perinatal outcomes cannot be fully measured in terms of days of hospitalization or financial considerations. There exists additionally the impact of transport of a newborn infant away from the mother, prolonged maternal-infant separation, and its sequelae.[16]

The fact that these assessments of fetal maturity are not being routinely performed has important regional implications. It may be considered the responsibility of a perinatal center to identify such problems and to strive for change by providing increased area-wide education and improved access to both consultative and laboratory facilities.

REFERENCES

1. Oong, L., Major, F., and Weingold, A.: Ultrasonic determination of fetal maturity at repeat cesarean section, Obstet. Gynecol. **38:** 294, 1971.
2. Gluck, L., Kulovich, M. V., Borer, R. C., Jr., et al: Diagnosis of the respiratory distress syndrome by amniocentesis, AM. J. OBSTET. GYNECOL. **109:** 440, 1971.
3. Gluck, L., and Kulovich, M. V.: Lecithin/sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancy, AM. J. OBSTET. GYNECOL. **115:** 539, 1973.
4. Usher, R., McLean, F., and Scott, K. E.: Judgement of fetal age. II. Clinical significance of gestational age and an objective method for its assessment, Pediatr. Clin. North Am. **13:** 835, 1966.
5. Amiel-Tison, C.: Neurological evaluation of the maturity of newborn infants, Arch. Dis. Child. **43:** 89, 1968.
6. Lubchenco, L., Hansman, C., and Boyd, E.: Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks, Pediatrics **37:** 403, 1966.
7. Hellegers, A., and Eastman, N.: The problem of prematurity—gravidas with cesarean section scars, AM. J. OBSTET. GYNECOL. **82:** 679, 1961.
8. Benson, R., Berendes, H., and Weiss, W.: Fetal compromise during elective cesarean section, AM. J. OBSTET. GYNECOL. **105:** 589, 1969.
9. Kafka, H., Hibbard, L., and Spears, R.: Perinatal mortality associated with cesarean section, AM. J. OBSTET. GYNECOL. **105:** 589, 1969.
10. Keettel, W., Randall, J., and Donnelly, M.: The hazards of elective induction of labor, AM. J. OBSTET. GYNECOL. **75:** 496, 1958.
11. Usher, R., Aller., A., and McLean, F.: Risk of respiratory distress syndrome related to gestational age, route of delivery and maternal disease, AM. OBSTET. GYNECOL. **111:** 826, 1971.
12. Frederick, J., and Butler, N.: Hyaline membrane disease, Lancet **2:** 768, 1972.
13. Farr, V., Kerridge, D., and Mitchell, R.: The value of some external characteristics in the assessment of gestational age at birth, Dev. Med. Child. Neurol. **8:** 657, 1966.
14. Coutts, N. A.: Neurological assessment of gestational age in low birthweight infants, Scott. Med. J. **16:** 398, 1971.
15. Dubowitz, L., Dubowitz, V., and Goldberg, C.: Clinical assessment of gestational age in the newborn infant, J. Pediatr. **77:** 1, 1970.
16. Klaus, M., and Kennell, J.: Mothers separated from their newborn infants, Pediatr. Clin. North Am. **17:** 1015, 1970.

The response of the human Fallopian tube to ergonovine and methyl-ergonovine in vivo

ELSIMAR M. COUTINHO, M.D.
HUGO MAIA, M.D.
LUSIA NASCIMENTO, M.D.
Salvador, Bahia, Brazil

Ergonovine maleate (EM) is a powerful stimulant of human tubal motility. It has been therefore thought that EM could interfere with normal ovum transport and serve as a contraceptive. The tube activating effects of EM and methyl EM were evaluated in 14 women and results confirmed that both are powerful stimulants of the human Fallopian tube. EM immediately post coitus significantly reduces the conception rate.

WE HAVE repeatedly reported that ergonovine maleate is a powerful stimulant of human tubal motility.[1–3] In studies carried out in women who had normal tubes and were operated on for tubal ligation, we found ergonovine maleate (EM) to be more potent than either prostaglandin $F_2\alpha$, norepinephrine, or oxytocin in inducing tubal contractions. The response to a single dose of 0.2 mg. of ergonovine maleate was prompt and long lasting, being recorded in some women for several hours.[2] In contrast to its effect on the Fallopian tube, the drug had poor stimulating action on the nonpregnant human myometrium.[3] In view of its unique effect on tubal motility, it has been thought that EM could interfere with normal ovum transport and serve therefore as a contraceptive.[1]

Pilot clinical trials carried out in our clinic, in which EM was given orally on a daily regimen, revealed that indeed the drug had a contraceptive effect. However, in view of several unexplained pregnancies which were considered contraceptive failures, it was felt that a more extensive knowledge of the effects of EM on the Fallopian tube was needed before a proper contraceptive regimen could be developed.

From the Department of Maternal Health and Child Care, Maternidade Climerio de Oliveira, Federal University of Bahia, School of Medicine.

Supported by the Ford Foundation, the Population Council, and the World Health Organization.

Received for publication June 19, 1975.

Accepted November 18, 1975.

Reprint requests: Dr. E. M. Coutinho, Maternidade Climerio de Oliveira, Universidade Federal da Bahia, Salvador, Bahia, Brazil.

We report here on studies carried out at Maternity Climerio Oliveira over the last 2 years, in which the tube-activating effects of EM and methyl EM were evaluated in 14 women of reproductive age. In order to allow evaluation of the hormonal effects on the response of the Fallopian tube to the ergot compounds, some women received sequential contraceptive therapy whereas others were treated with selected progestins.

Materials and methods

Six women in this series had tubal occlusion and were operated on for restoration of tubal patency. Five women had normal tubes and required tubal ligation. The other three subjects were multiparous women whose tubal activity was recorded following a cesarean section.

Six subjects were treated with contraceptive steroids following control cycles in which the effect of the ergot compounds was tested. Two subjects received a sequential contraceptive, the treatment consisting of daily administration of mestranol (50 μg) for 11 days, followed by daily administration of Mestranol (50 μg) plus norethindrone* (1 mg.). Two subjects received the progestin ethynodiol diacetate† (500 mcg.) daily, continuously for 30 days. Medroxyprogesterone acetate (Depo Provera‡) (50 mg.) was administered as a single intramuscular injection to two other subjects.

In all cases tubal motility was evaluated by recording intratubal pressure with a microballoon as described previously.[4] Uterine motility was also recorded by

*Novulon S., Johnson & Johnson do Brasil, S. Paulo, Brazil.
†Searle do Brasil, S. Paulo, Brazil.
‡The Upjohn Company, Kalamazoo, Michigan.

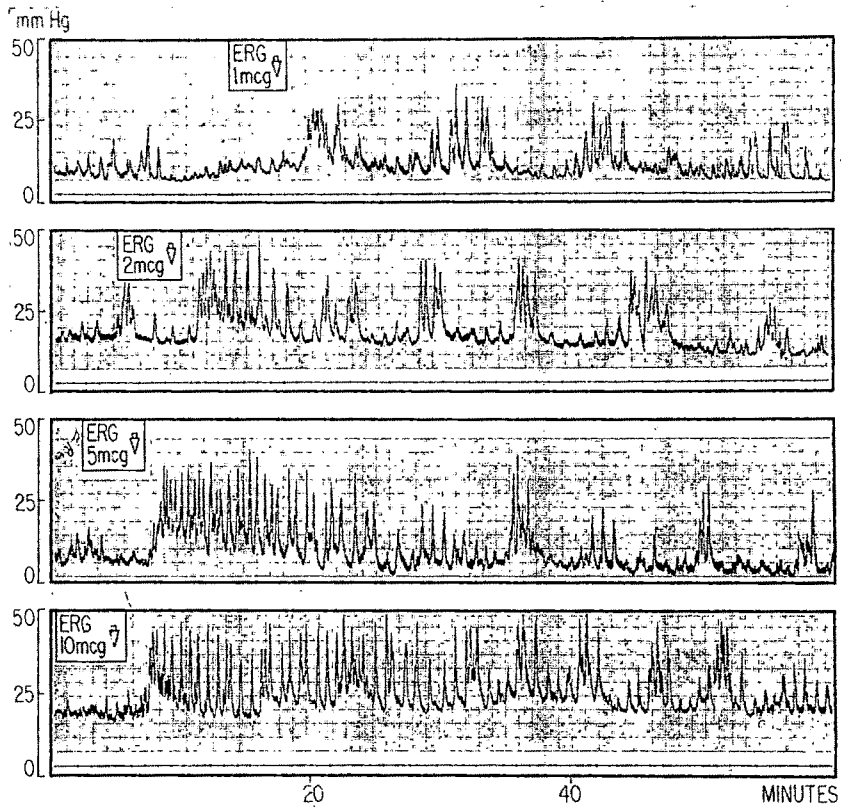


Fig. 1. Response to graded doses of EM in same subject on day 5 of menstrual cycle.

intrauterine microballoons. Recordings were made every other day for 1 to 2 months, starting 2 to 3 days following laparotomy. EM* was given by either mouth or intramuscular injection, whereas methyl EM† was always given by intramuscular or intravenous injection.

In view of the relatively small number of cases in each category and the marked similarity of the tubal response to ergonovine in subjects from different groups, no attempt was made to analyze quantitatively the pharmacologic response.

Results

A dose of 0.1 to 0.2 mg. of either EM or methyl EM induced a marked increase in tubal motility which lasted from 30 minutes to several hours in all subjects. The effect lasted longer in some women than in others but in most cases the response to a single administration of the standard dose of 0.2 mg. of EM or methyl EM could be recorded for approximately 4 to 5 hours. Both the intensity and duration of the response were lessened when smaller doses were used, but a significant activation of tubal motility could be induced with an intravenous injection of as little as 1 μg of EM. Fig. 1 shows the response to graded doses of EM in the same subject on day 5 of the menstrual cycle.

The response to EM or to methyl EM could be elicited at all stages of the menstrual cycle. The effect was more pronounced and lasted longer during menstruation than during the proliferative phase of the cycle. The response was less marked during midcycle, being weakest during the early luteal phase. Fig. 2 shows the response to EM recorded in the same subject at different phases of the menstrual cycle.

In two subjects to whom EM and methyl EM were administered daily for two consecutive menstrual cycles, the response elicited during the second cycle was of the same magnitude as that recorded at corresponding phases of the first cycle.

All segments of the tube responded to the ergot alkaloids. In women who had three pressure receptors which allowed recording from three different portions of the tube (isthmus and proximal and distal ampulla), full activation was recorded (Fig. 3) following injection or oral administration of either EM or methyl EM.

In patients treated with sequential contraceptive steroids, the response to EM was recorded throughout the treatment cycle. Fig. 4 shows the response during

*Ergotrate, Eli Lilly Co., Indianapolis, Indiana.
†Methergine, Sandoz, Basle, Switzerland.

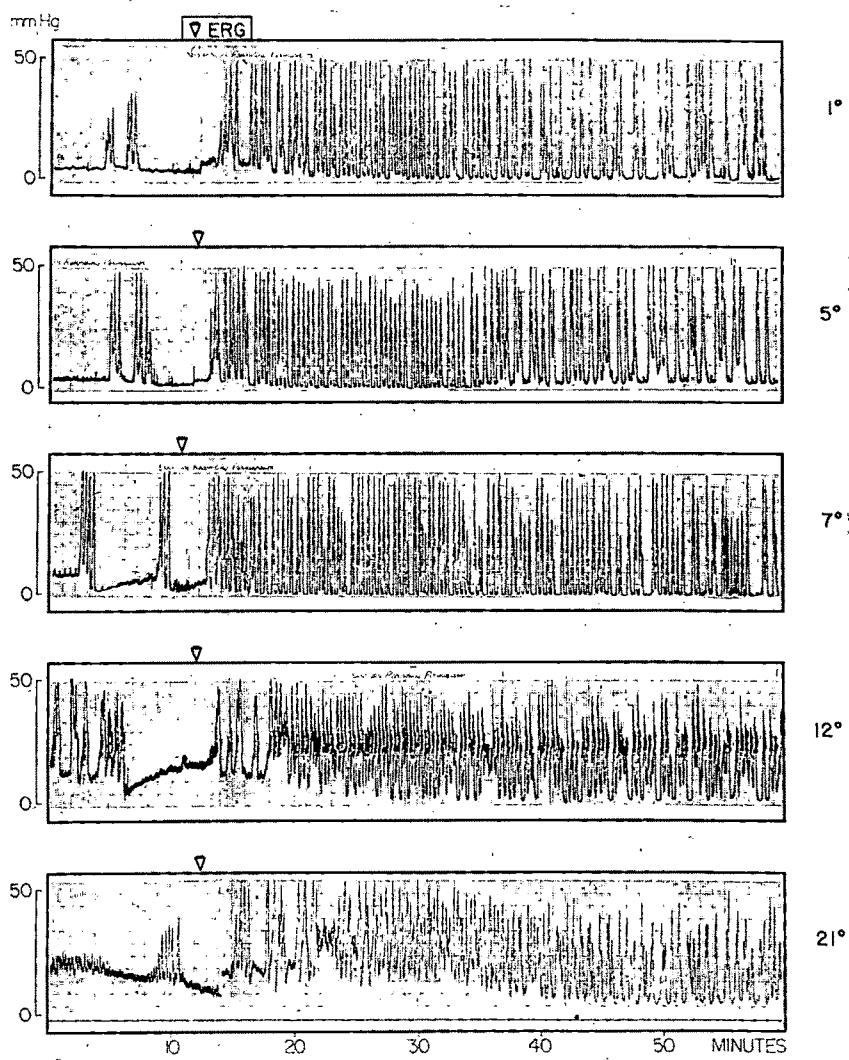


Fig. 2. Response to EM in same subject at different phases of menstrual cycle.

the estrogenic phase of the treatment and Fig. 5 shows the response during combined estrogen-progestin phase of the treatment. In subjects treated with the norsteroid ethinodiol diacetate continuously, the effects of both EM and methyl EM were undiminished as illustrated in Fig. 6, where tubal activity and the tubal response to EM in a subject who received 500 μg of ethynodiol diacetate for 20 days is shown. In subjects treated with medroxyprogesterone acetate (Depo Provera), there was a reduction in both the intensity and duration of the response to the ergot compounds. Fig. 7 shows the effect of EM 10 days after the injection of 50 mg. of Depo Provera.

The tubal response to orally administered EM occurs 10 to 60 minutes following ingestion of the drug, but lasts as long as or longer than the response to EM injections. In fasting subjects the time interval between ingestion and response is shorter than in nonfasting subjects, and the intensity of the response is much greater. In some nonfasting subjects no significant response was recorded for as long as 3 hours. Fig. 8 shows the response of the Fallopian tube and the uterus to orally administered EM during the luteal phase of the cycle.

Comment

The present study confirms our previous reports that ergot compounds such as EM and methyl-EM are powerful stimulants of the human Fallopian tube.[1–3] It is remarkable that the same compounds are ineffective on the oviduct of other species, such as the rabbit,[5] and their utero stimulant effect in nonpregnant women is comparatively weak.[1] From our present study it is not possible to identify with precision the site of action of the ergot alkaloids on the tube, but from the appearance of the mechanical response, it seems likely that

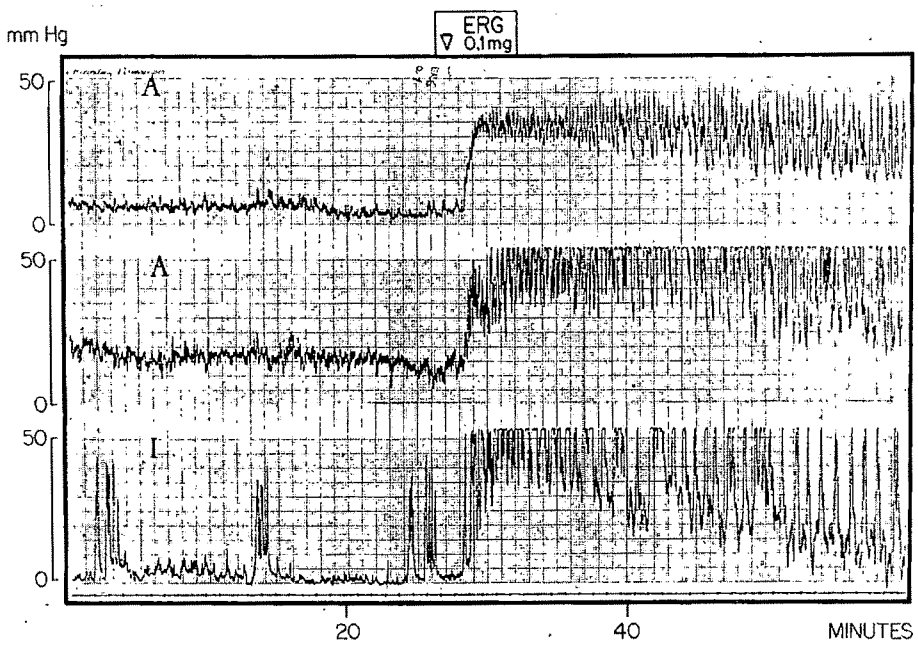


Fig. 3. Response to injection of EM.

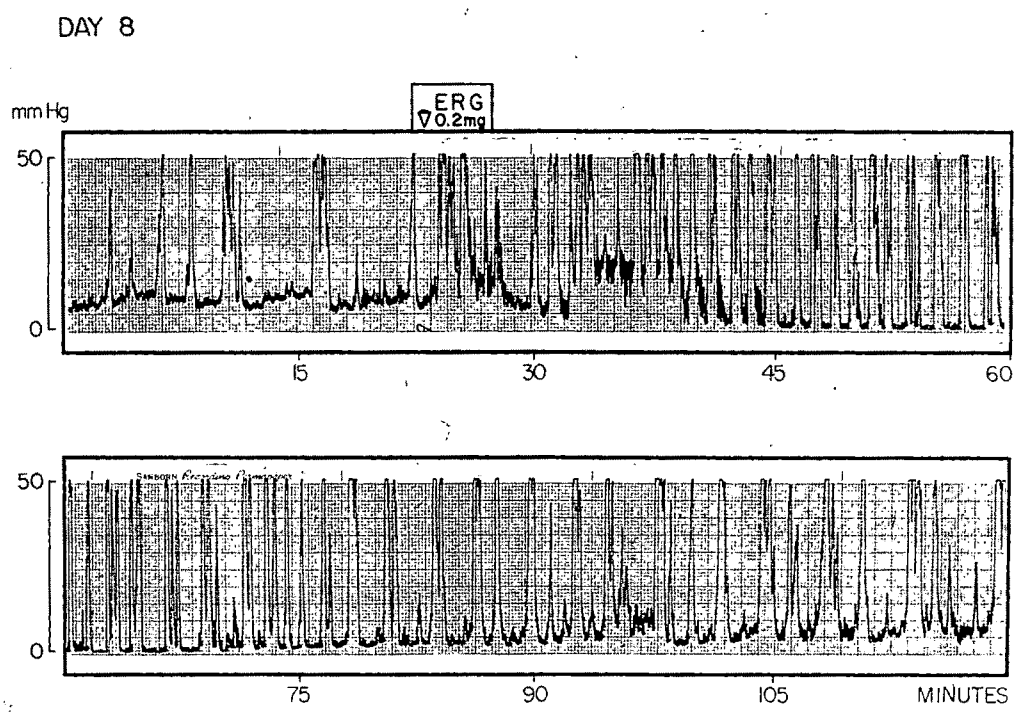


Fig. 4. Response to EM during estrogenic phase of treatment.

both longitudinal and circular musculature on the tubal wall are activated. Activation of associated structures such as the mesosalpinx and even the uterus may also contribute to the over-all mechanical response.

The response of the tube to EM and methyl EM has some analogies to the tubal response to norepinephrine infusions.[6] Although the ergot alkaloids are considered alpha-adrenergic blocking agents, they may act as adrenergic agonists, with intrinsic activity decreasing and blocking activity increasing from ergotamine to the dehydrogenated derivatives of ergotoxine.[7] The mechanism of action of EM and methyl EM may involve blockade of neuronal re-uptake of locally

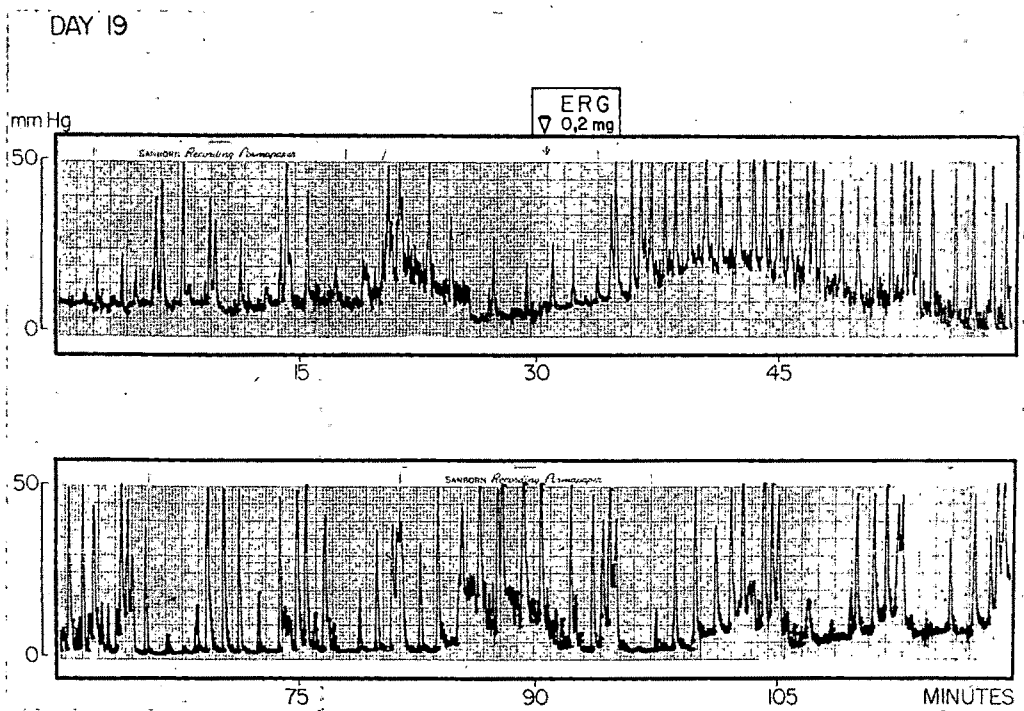


Fig. 5. Response to EM during combined estrogen-progestin phase of treatment.

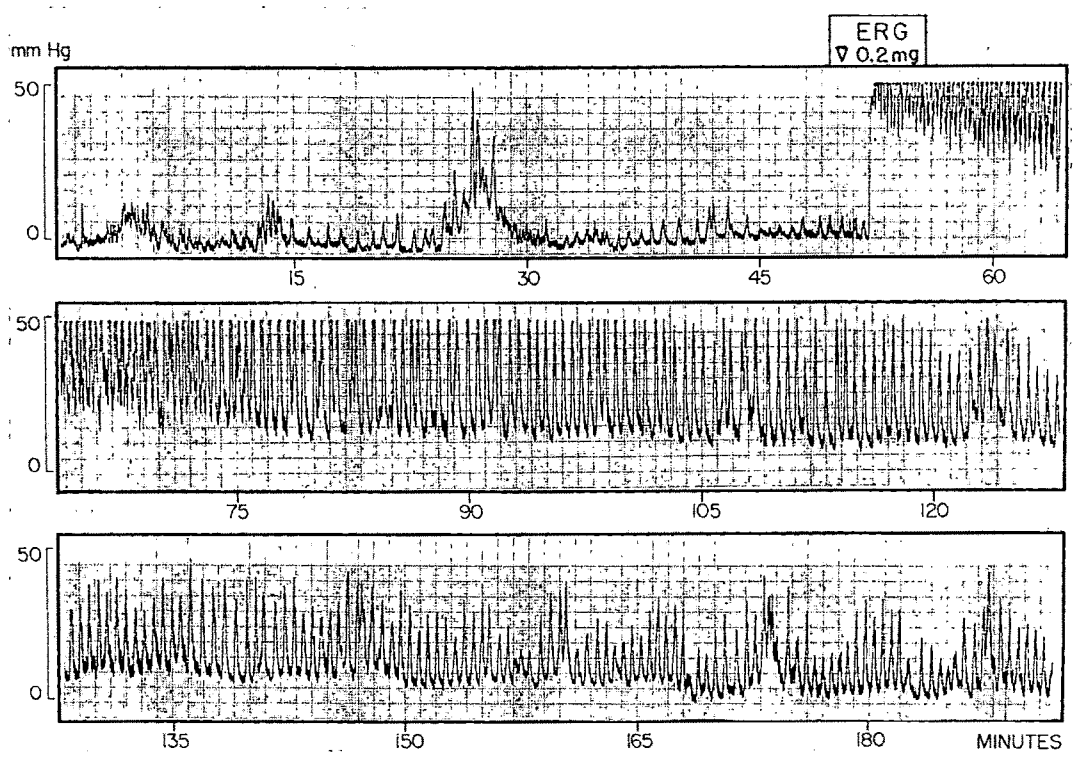


Fig. 6. Effect of EM and methyl EM in subjects treated with norsteroid ethynodiol diacetate continuously.

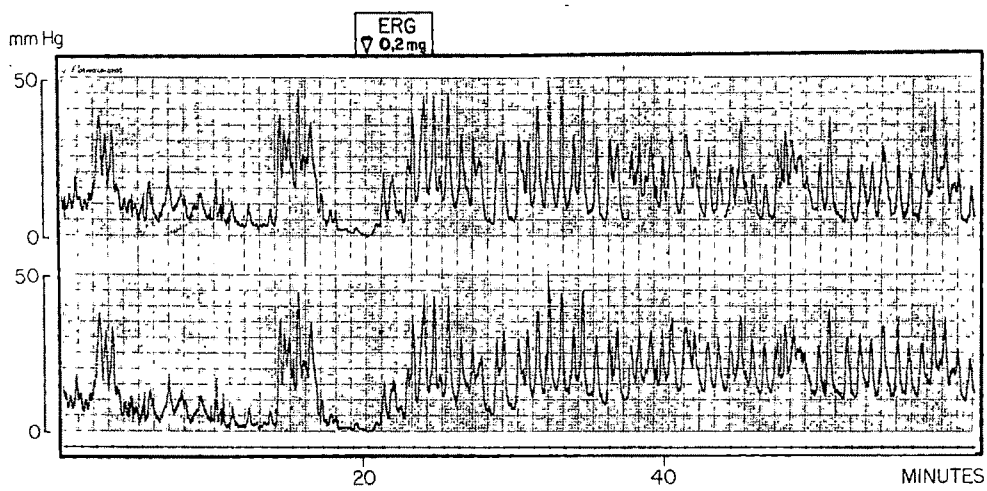


Fig. 7. Effect of EM 10 days after injection of Depo-Provera.

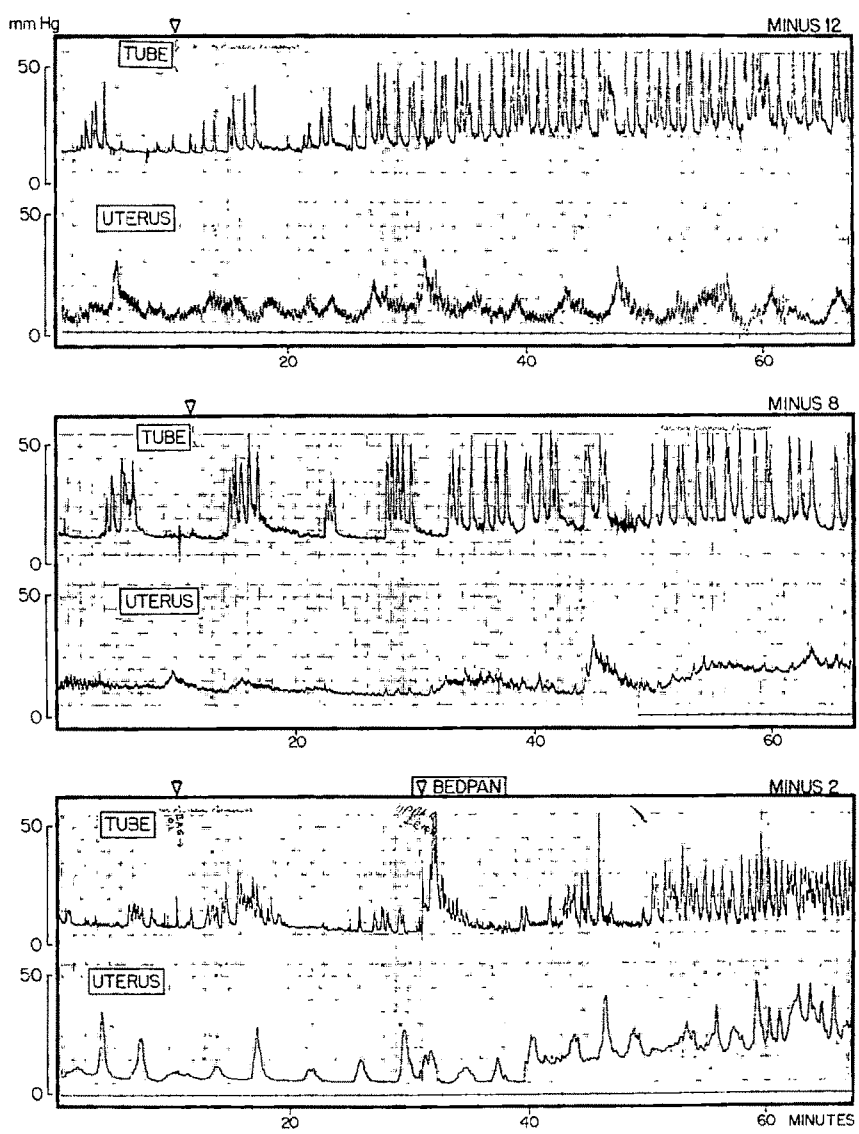


Fig. 8. Response of Fallopian tube and uterus to orally administered EM during luteal phase of cycle.

released norepinephrine, a phenomenon which seems to also occur in the Fallopian tube of women following the injection of alpha-adrenergic blocking agents such as phenoxybenzamine and phentolamine. In the human subject, phentolamine activates human tubal activity while blocking the alpha-adrenergic response in the uterus and in vascular smooth muscle.[2] In the rabbit oviduct, on the other hand, these compounds act as true alpha-adrenergic receptor blockers, not only suppressing the response to alpha-adrenergic agonists but also inhibiting spontaneous tubal activity.[5]

The present studies show that the motility of all segments of the tube can be activated repeatedly with either EM or methyl EM. The reproducibility of the response throughout the study period suggests, on the other hand, that it may be possible to use the ergot compounds for long-term activation of tubal motility.

Although the powerful contractions induced by EM and methyl EM should be adequate to interfere with ovum transport, it is not known whether activation of tubal motility by ergot alkaloids is sufficient to achieve expulsion of the egg into the uterus or to cause enough damage to prevent normal ovum development.

Studies now in progress suggest that EM reduces significantly the conception rate in women when the drug is administered immediately post coitus.

As ergonovine and methyl ergonovine are among the less toxic of the ergot compounds,[8] they may probably be used without danger of developing ergotism.

REFERENCES

1. Coutinho, E. M.: Tubal and uterine motility, *in* Diczfalusy, E., and Borell, V., editors: Nobel Symposium 15: Control of Human Fertility, Stockholm, 1971, Almqvist & Wiksell; New York, 1971, John Wiley & Sons.
2. Coutinho, E. M.: Fertil. Steril. **22:** 807, 1971.
3. Coutinho, E. M.: Hormonal control of tubal musculature, *in* Segal, S., Corfman, P., Crozier, R., and Condliffe, P., editors: Regulation of Mammalian Reproduction, Springfield, Ill., 1973, Charles C Thomas, Publisher.
4. Maia, H., and Coutinho, E. M.: Am. J. Obstet. Gynecol. **102:** 1043, 1968.
5. Coutinho, E. M., Mattos, C. E. R., and da Silva, A. R.: Fertil. Steril. **22:** 311, 1971.
6. Coutinho, E. M., Maia, H., and Filho, J. A.: Fertil. Steril. **21:** 500, 1970.
7. Innes, I. R.: Br. J. Pharmacol. Chemother. **19:** 120, 1962.
8. Brazeau, P.: (1970) Drugs affecting uterine motility, *in* Goodman, L. S., and Gilman, A., editors: The Pharmacological Basis of Therapeutics, New York, 1970, The Macmillan Company.

Erratum

In the article, "Drug addiction in pregnancy and the neonate," by George Blinick, M.D., Robert C. Wallach, M.D., Eulogio Jerez, M.D., and Bruce D. Ackerman, M.D., in the May 15, 1976, issue of the Journal, page 137, in the first line of the second paragraph, "With the institution of outpatient centers which provide rapid induction of labor, . . . " should have been, "With the institution of outpatient rapid induction centers, ..."

Suboptimal pregnancy outcome among women with prior abortions and premature births

STEVE J. FUNDERBURK, M.D.
DONALD GUTHRIE, PH.D.
DAVID MELDRUM, M.D.
Los Angeles, California

Data from 25,958 consecutive UCLA deliveries were analyzed to determine the effect of prior abortions and premature births on current pregnancy outcome. Perinatal death rate, combining stillbirths and neonatal deaths, increased more than threefold among women with at least one prior premature birth and at least one prior abortion and approached 18 per cent of current deliveries when there were three or more prior premature births. Abnormal live births, defined as infants with either birth weight under 2,501 grams, gestational age less than 37 weeks, or congenital anomalies, significantly increased as the number of prior abortions and premature births increased, each in a range of 0 through 3 or more. For example, among women with at least three prior premature births, there were greater than 50 per cent abnormal live births. The risk was mostly that of low birth weight and low gestational age, although there was a slight increase in congenital anomalies. The risk was reduced considerably when there were previous term births and was influenced variably by race, clinic classification, maternal illness, and prior pregnancy complications. This empirical data on pregnancy outcome should be useful in reproductive counseling among women with pregnancy losses and premature births.

EARLIER STUDIES have shown that an obstetric history of abortions, premature births, and perinatal deaths increases the subsequent rate of fetal loss, prematurity, and perinatal death. The British Perinatal Mortality Study showed that a past history of abortion increased the neonatal mortality rate by 50 per cent, that the past history of a premature liveborn infant doubled the over-all risk of perinatal death to subsequent infants and that any previous stillbirth or neonatal death multiplied the over-all risk 2.6 times.[3] Risk to subsequent infants in that study considered only death and did not examine prematurity and low birth weight per se nor congenital anomalies. The Pregnancy Outcome Study from the Health Insurance Plan of Greater New York revealed that one third of current pregnancies were affected by either fetal death, low birth weight, or congenital anomalies for women whose last prior pregnancy ended in either a prematurely born infant or fetal death.[16] The Ontario Perinatal Mortality Study[12] revealed a combined effect on the mortality rate when the history included both premature births and abortions. In a Greek population, a previous history of spontaneous abortions alone was shown to double the frequency of premature births and stillbirths.[13] Among a Pakistani population, the combined frequency of fetal loss and perinatal death doubled with a similar history of wastage of one pregnancy and this risk increased with a history of wastage of two or more pregnancies.[1] The collaborative perinatal study of the National Institute of Neurological Diseases and Stroke[11] revealed that among whites, the incidence of low birth weight was 1 in 4 and among blacks 1 in 3 when the last prior child was under 2,501 grams.

From the Child Psychiatry and Mental Retardation Program, Department of Psychiatry, and Department of Obstetrics and Gynecology, NPI-UCLA Center for the Health Sciences.

This research supported in part by: University of California at Los Angeles; Mental Retardation Program and Child Psychiatry Program, NPI-UCLA, MCH-927; Interdisciplinary Training in Mental Retardation, HD-04612; Mental Retardation Research Center, UCLA, HD-00345; Research Training in Mental Retardation, HD-05615; Developmental Biology in Mental Retardation.

Received for publication August 21, 1975.

Accepted November 18, 1975.

Reprint requests: Steve J. Funderburk, M.D., NPI-UCLA Center for the Health Sciences, 760 Westwood Plaza, Los Angeles, California 90024.

Table I. Pregnancy outcome in present study compared to previously reported studies

Abnormality	*Rate per 1,000 live births**		
		Present study	
	Previously reported	*All live births*	*Prior premature births ≥ 1 and prior abortions ≥ 1*
		N† = 25,575	N = 369
(a) Birth weight <2,501 grams	59.0[16]	63.9	162.0
(b) Anomalies, neonatal detection	20.0[7]	15.7	19.0
(c) Gestational age <37 wk.	—	50.3	158.5
Total abnormal (a) + (b) + (c)	—	95.3	221.3
Neonatal death	9.8[16]	10.0	35.2
		N = 25,958	N = 387
Perinatal death per 1,000 deliveries	29.35[5]	23.7	80.1

*Birth weight > 500 grams and gestation > 24 wk.
†N = Total live births or deliveries.

Table II. Perinatal death rate according to the number of prior abortions and premature births

Pregnancy history		*No. of deliveries*	*Perinatal deaths per 1,000 deliveries*		
			Stillborn	*Neonatal death*	*Total*
Abortions	0	21,168	10.0	10.1	20.0
	1	3,389	21.0	13.0	33.9
	2	876	30.8	12.6	43.4
	≥3	525	43.8	26.7	70.5
Chi square					$p < 0.0001$
Premature births	0	24,808	11.6	10.1	21.7
	1	924	27.1	24.9	51.9
	2	147	74.8	27.2	102.0
	≥3	79	101.3	75.9	177.2
Chi square					$p < 0.0001$
Prior premature births and prior abortions	≥1 ≥1	387	41.3	38.8	80.1

These previous studies have not quantitated the severity of effect on pregnancy outcome beyond a history of two or more fetal losses, perinatal deaths, or premature births, and they have not fully examined the compounding effect of other obstetric variables. The purpose of the current study is to determine the empirical effect on pregnancy outcome of an increasing number of prior abortions and premature births, individually and combined. An additional purpose is to determine whether other maternal factors such as number of term deliveries and socioeconomic status further influence pregnancy outcome among women with prior fetal losses and low-birth-weight infants.

The usefulness of this study in counseling couples with suboptimal reproductive histories is evident. Increasingly, patients with prior abortions and perinatal deaths are being referred to the UCLA Genetics Clinic for diagnosis and prognostic counseling. Their concern is both for the financial and psychological burden of repeat pregnancy wastage, and perhaps even more important for the likelihood of suboptimal status among future viable neonates. This study also may lend clues to etiology and to preventive measures by the analysis of additional maternal factors which further influence pregnancy outcome among women with prior reproductive abnormalities.

Method

Data were obtained on 25,958 consecutive deliveries at the UCLA Department of Obstetrics and Gynecol-

ogy from April, 1963, through June, 1974. At the time of delivery, a data file was completed on each delivery by review of maternal and neonatal charts. Physicians were questioned when obstetric and neonatal records were incomplete. Multiple births were deleted from this study. A sample of newborn and maternal charts, selected from deliveries with maternal histories of previous abortions and premature births, were reviewed to verify accuracy of the data collection and retrieval. The influence of previous abortions and premature births on pregnancy outcome was examined from two perspectives. First, the perinatal mortality rate was determined by combining the incidence of stillbirths and neonatal deaths among current deliveries. Second, the rate of potentially abnormal viable offspring was determined by combining the incidence of either low birth weight, low gestational age, or congenital anomalies, among live births. Stillbirths were defined as antepartum or intrapartum deaths plus deliveries of all fetuses of gestational age less than 25 weeks or birth weight less than 501 grams. Live births were defined as liveborns with gestational age greater than 24 weeks and birth weight greater than 500 grams. Low birth weight was defined as birth weight under 2,501 grams and low gestational age as gestational age under 37 weeks.

Results

Review of 60 neonatal charts revealed accurate data collection from each for birth weight, gestational age, and neonatal survival. Two unrecorded congenital anomalies were present, one case of hydrocele and one case of cryptorchidism, giving a total of eight anomalies among 60 live births. Neonatal asphyxia was coded for several infants who had very mild and transient respiratory difficulty and, therefore, was not further evaluated. Review of 55 maternal records, all coded as having at least one prior abortion and at least one prior premature birth, not unexpectedly revealed coding of late fetal losses as premature births in five cases. This was not considered a true inconsistency since late abortions and early premature births conceivably have similar biologic significance. Given this limitation, and since only two mothers had a history of less than two fetal losses, the over-all data error for previous pregnancy outcome was considered less than 2 per cent. There was just one example of a therapeutic abortion. Apparently there were few induced abortions among these women with prior pregnancy wastage, although unfortunately prior abortions were not further specified in the coded data.

The proportion of infants with low birth weight, congenital anomalies, and neonatal death among all

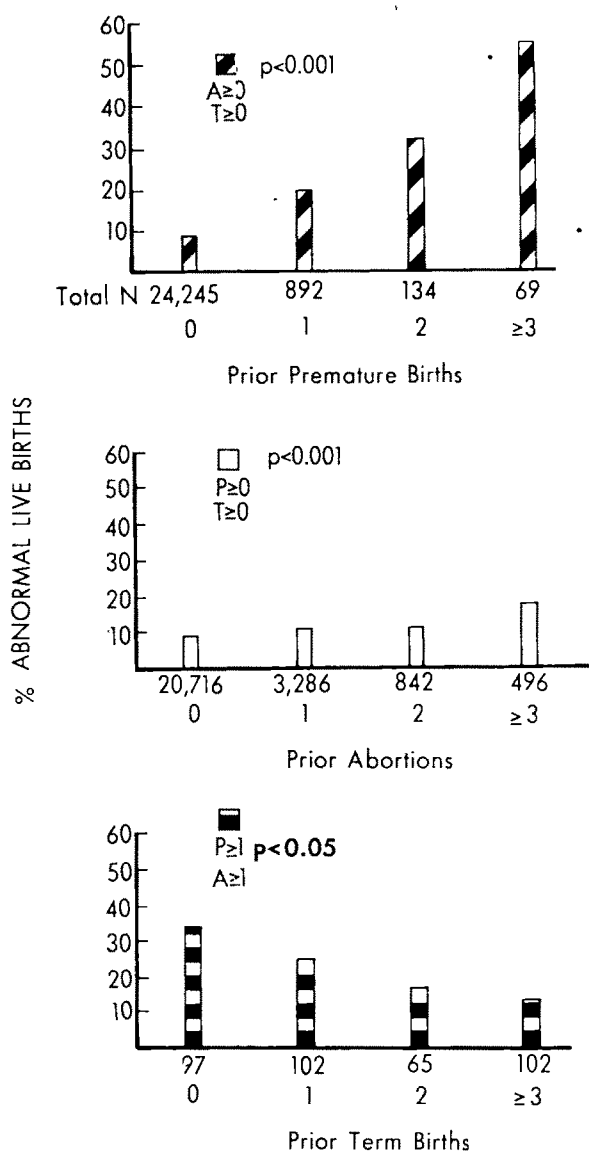


Fig. 1. Shown here is the effect of prior premature births *(P)*, and prior abortions *(A)*, among all live births and the effect of prior term term births *(T)*, when there was at least one prior abortion and at least one prior premature birth.

live births and the proportion of perinatal deaths among all deliveries was found to be similar to that previously reported (Table I). The combined effect of prior abortions and premature births is shown in the column to the right.

The perinatal death rate was shown to steadily increase as the number of prior abortions and premature births increased (Table II).

The compounding effect of several obstetric variables in addition to prior abortions and premature births is shown in Table III. The presence of any prior pregnancy complication, found in more than 50 per

Table III. Obstetric correlates for abnormal live births among women with prior premature births and prior abortions

	Per cent abnormal live births per category*					*Chi square*
Total (369)			22.13			
Maternal variable						
Marital status:	*Married*	*Single*	*Separated*	*Widowed*	*Divorced*	N.S.†
	22.19	0.0	23.81	100.0	26.67	
Clinic classification:	*UCLA clinic*	*Unregistered*	*County Health Clinic*	*Private referrals*	*Private non-referrals*	
	24.64	20.00	16.28	24.49	10.0	N.S.
Race:	*Caucasian*		*Black*	*Spanish Surname*		
	23.86		34.21	8.06		$p < 0.05$
Prior pregnancies	*0*	*1*	*2*	*≥3*		
Term:	31.96	22.55	18.46	14.71		$p < 0.05$
Premature:	—	18.73	22.64	53.33		$p < 0.001$
Abortion:	—	18.64	23.17	32.81		$p \sim 0.05$
Perinatal death:	24.24	13.75	0.0	50.00		N.S.
Prior pregnancy		*Yes*		*No*		
complications (207):		27.32		15.53		$p < 0.01$
Toxemia (28):		17.86		22.49		N.S.
Prior illness (99):		30.30		19.10		$p < 0.05$
Diabetes (10):		40.00		21.64		N.S.

*a) + b) + c) from Table I.

†Not significant (number live births per category).

cent of the mothers and including toxemia, hemorrhage, excess size of infant, or fetal abnormality, significantly correlated with an increased proportion of abnormal live births. Similarly, the pre-existence of any maternal illness, found in approximately 25 per cent and including diabetes, hypertension without toxemia, infertility, endocrine or neurologic disturbance, and disease of the heart, lungs, or kidneys, significantly correlated with an increased proportion of abnormal live births.

The highest rates of abnormal live births occurred when there were three or more prior premature births (Fig. 1). The effect of prior abortions was less but did significantly correlate with abnormal pregnancy outcome, and among women with at least one prior premature birth and at least one prior abortion, an increasing number of term births correlated with improved pregnancy outcome. Further analysis of the data, not shown in Fig. 1, revealed that the high risk of prior premature births was not augmented by an additional history of abortions, but that the significant affect of prior abortions remained even for women with no prior premature births. Table IV shows that, in contrast to all low-birth-weight infants, congenital anomalies did not increase for the low-birth-weight infants among women with prior premature births and prior abortions and that neonatal death correlated with low birth weight regardless of the past pregnancy history.

Comment

This study revealed a greater than threefold increase in perinatal death among women with at least one prior premature birth and at least one prior abortion. For women with three or more previous premature births, the perinatal death rate approached 18 per cent of their current deliveries. Among the live births of women with at least one previous premature birth and at least one previous abortion, the proportion of low birthweight infants was 2.5 times greater, the malformation rate only slightly greater, and the incidence of low gestational age three times greater than the corresponding rates among all live births. The number of liveborn infants with either low birth weight, low gestational age, or congenital anomalies was 2.3 times increased. The proportion of abnormal liveborn infants increased to more than 50 per cent when there were three or more previous premature births. Interestingly, the slightly increased rate of congenital anomalies was not among low-birth-weight infants, since only one infant of women with prior premature births and prior abortions had both anomalies and low birth weight.

An important finding in this study was that the presence of any prior term births significantly reduced the risk of prior abortions and premature births. Other obstetric factors such as race, private versus nonprivate classification, prior pregnancy complications, and maternal illnesses had variable effects on pregnancy

Table IV. Rate of anomalies and neonatal deaths according to birthweight

*Live births**	*No.*	*Per cent*	*Anomalies* %	*Neonatal death* %
Total	25,575	(100)	1.6	1.0
<2,501 Gm.	1,618	(6.3)	4.5	11.1
<1,501 Gm.	218	(0.8)	6.0	52.7
Chi square			$p < 0.0001$	$p < 0.0001$
Prior premature births ≥ 1 and prior abortions ≥ 1				
Total	369	(100)	1.9	3.5
2,501 Gm.	59	(16.0)	1.7	16.9
1,501 Gm.	11	(3.0)	0	45.4
Total abnormal†	81	(22.0)	8.6	16.1
Chi square			—	$p < 0.0001$

*As defined in Table I.

†a) + b) + c) from Table I.

outcome among women with prior abortions and premature births.

In this study, 16 per cent of the abnormal infants born to women with prior premature births and abortions died in the neonatal period. This increased neonatal mortality rate correlated with low birth weight and the neonatal mortality rate was equally high among low-birth-weight infants regardless of whether there were previous abortions or premature births. Quality of survival continues to be of concern among low-birth-weight infants because of possible learning difficulties and behavioral disorders,[15] although numerous studies indicate improvement in the prognosis for normal development of low-birth-weight infants.[6]

The etiology of recurrent fetal loss and premature births largely remains obscure. Chromosome aberrations have been found in only a small proportion of parents with previous recurrent pregnancy failure.[4, 18] A cytogenetic study of two consecutive abortuses revealed a tendency for chromosome abnormality to recur but no abnormalities were found among subsequent term pregnancies.[2] In another study, malformations were found in a large proportion of abortuses and stillbirths, with 17 and 47 per cent of the malformations among abortuses and stillbirths, respectively, due to genetic failures.[14] It should be noted that the previous cytogenetic studies on parents did not utilize new banding techniques. A recent study utilizing a banding technique revealed a chromosome abnormality in 16 of 27 abortuses.[8] Other factors including potential role of genital mycoplasmas in the etiology of prematurity and low birth weight, and the established relationship of maternal smoking with increased perinatal death and reduced birth weight, have recently been reviewed.[9, 10] The history of maternal smoking unfortunately was not available in the data of the current study.

Pregnancy wastage has been shown to be higher when there is inadequate antenatal care.[1] In addition, it is now clear that pregnancy weight and weight gain during pregnancy correlate positively with term infant birth weight.[17] Presumably better nutrition and attention to maternal illnesses will improve pregnancy outcome. In our study, the relatively good current pregnancy outcome among Spanish-surname women with prior abortions and premature births perhaps reflects improved socioeconomic status associated with recent immigration. The degree of early antenatal care, current pregnancy complications, and maternal illness among women without previous abortions and premature births will be examined in a subsequent report.

We are indebted to Angel Hernandez, Jr., Linda Rosenberg, and Sharon McCormick for their technical computer assistance.

REFERENCES

1. Awan, A. K.: Some biological correlates of pregnancy wastage, Am. J. Obstet. Gynecol. **119:** 525, 1974.
2. Boue, J., and Boue, A.: Chromosomal analysis of two consecutive abortuses in each of 43 women, Humangenetik **19:** 275, 1973.
3. Butler, N., and Bonham, D.: Perinatal mortality. Edinburgh, 1963, E. & S. Livingstone, Ltd., p. 288.
4. Harris, H., and Hirschhorn, K., editors: Chromosomes and abortions, Adv. Human Genet. **2:** 201, 1971.
5. Clifford, S.: High-risk pregnancy. I. Prevention of prematurity the sine qua non for reduction in mental retardation and other neurologic disorders, N. Engl. J. Med. **271:** 243, 1964.
6. Davies, P., and Stewart, A.: Low-birth-weight infants:

Neurological sequelae and later intelligence, Br. Med. Bull. **31:** 85, 1975.
7. Marden, P., Smith, D., and McDonald, M.: Congenital anomalies in the newborn infant, including minor variations, J. Pediatr. **64:** 357, 1964.
8. McConnell, H., and Carr, D.: Recent advances in the cytogenetic study of human spontaneous abortions, Obstet. Gynecol. **45:** 547, 1975.
9. McCormack, W., Braun, P., Yhu-Hsiung, L., Klein, J., and Kass, E.: The genital mycoplasmas, N. Engl. J. Med. **288:** 78, 1973.
10. Meyer, M., Tonascia, J., and Buck, C.: The interrelationship of maternal smoking and increased perinatal mortality with other risk factors, Am. J. Epidemiol. **100:** 443, 1975.
11. Niswander, K., and Gordon, M.: Women and their pregnancies, U. S. Dept. HEW, PHS, NIH, pp. 185-197, 1972.
12. Ontario Department of Health: Supplement to the Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals. Ontario Perinatal Mortality Study Committee, Toronto, Canada, 1967.
13. Pantelakis, S., Papadimitriou, G., and Doxiadis, S.: Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies, AM. J. OBSTET. GYNECOL. **116:** 799, 1973.
14. Poland, B., and Lowry, R.: The use of spontaneous abortuses and stillbirths in genetic counseling, AM. J. OBSTET. GYNECOL. **118:** 322, 1974.
15. Rubin, R., Rosenblatt, C., and Balow, B.: Psychological and educational sequelae of prematurity, Pediatrics **52:** 352, 1973.
16. Shapiro, S., Ross, L., and Levine, H.: Relationship of selected prenatal factors to pregnancy outcome and congenital anomalies, Am. J. Public Health **55:** 268, 1965.
17. Simpson, J., Lawless, R., and Mitchell, C.: Responsibility of the obstetrician to the fetus, Obstet. Gynecol. **45:** 481, 1975.
18. Stenchever, M., and Jarvis, J.: Cytogenetic studies in reproductive failure, Obstet. Gynecol. **37:** 83, 1971.

The Robert S. Hotchkiss Symposium on Basic and Practical Aspects of the Diagnosis and Treatment of Male Infertility

A postgraduate course, "The Robert S. Hotchkiss Symposium on Basic and Practical Aspects of the Diagnosis and Treatment of Male Infertility," will be given on Saturday and Sunday, October 9 and 10, 1976, at the New York University Post-Graduate Medical School. This course will provide a practical guide to the physician evaluating and treating the infertile male subject. It will present in a rational and workable form the latest knowledge and most effective methods of diagnosing and managing male infertility problems, with consideration in depth of basic reproductive physiology and pathophysiology. Experts will present current concepts in the field. Ample time has been allotted for questions and discussion.

The course will be of value to anyone dealing with the complexities of the infertile couple and will also provide competence in this field now demanded by certifying boards in urology, reproductive gynecology, endocrinology, and the primary practice specialties.

Dr. Richard D. Amelar, Clinical Professor of Urology, is Course Director.

This continuing medical education offering meets the criteria for 13 hours of credit in Category I for the Physicians' Recognition Award of the American Medical Association.

A tuition fee of $150.00 is payable when application is submitted. There is a 25 per cent reduction in tuition ($112) for current residents in training.

Further information and applications may be obtained from: The Office of Associate Dean, N.Y.U. Post-Graduate Medical School, 550 First Ave., New York, New York 10016. Telephone: (212) 679-3200, Ext. 4207.

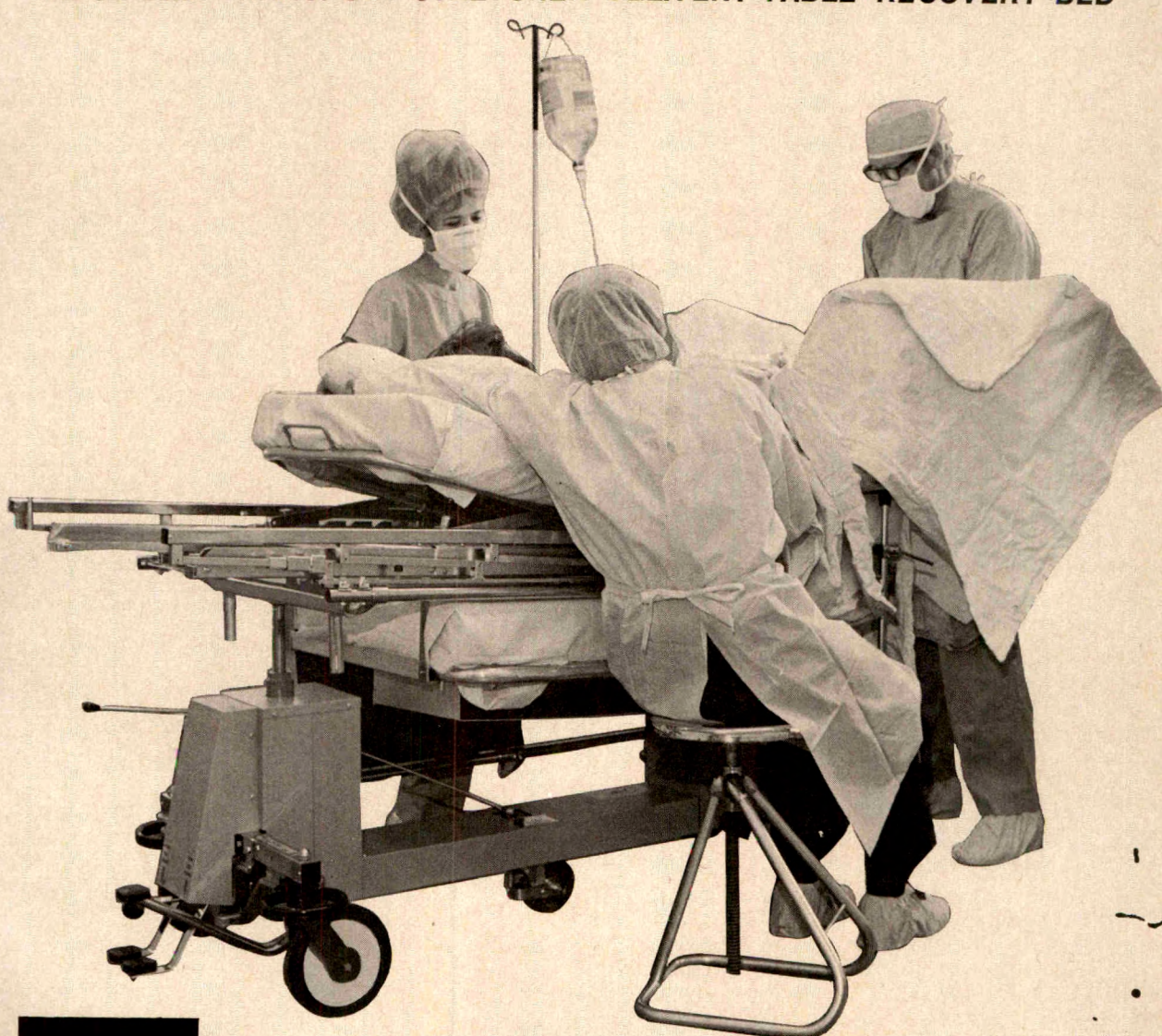
Stryker®

LtD+1®

A complete OB patient handling and care system

- **Patient comfort . . . .** no need to transfer patient
- **Collapsible siderails . . . .** out of the way during delivery, but provide security during transport
- **La Maze positioning . . . .** hydraulic, foot-controlled jacks allow a wide variety of positioning choices
- **Total monitoring convenience . . . .** large storage area allows most monitors to be moved with patient

LABOR BED•TRANSPORT STRETCHER•DELIVERY TABLE•RECOVERY BED



Stryker®

CALL COLLECT 616/381-3811, EXT. 272

STRYKER CORPORATION / 420 Alcott Street / Kalamazoo, Michigan 49001

Immediate opening for qualified Ob-Gyn position in southeastern Arizona. Excellent potential in fast growing community. Ideal weather and sports activity. Well equipped hospital with excellent staff. Please send inquiries to:

Mr. John R. Lally, Administrator
Sierra Vista Community Hospital
300 El Camino Real S. E.
Sierra Vista, Arizona 85635

THE UNIVERSITY OF MELBOURNE DUNBAR HOOPER CHAIR OF OBSTETRICS AND GYNAECOLOGY

Applications are invited for the Dunbar Hooper Chair of Obstetrics and Gynaecology at the Royal Women's Hospital. This Chair will become vacant on 1 January, 1978, on the retirement of its first occupant, Professor Sir Lance Townsend.

The appointee must be eligible for registration as a medical practitioner in Victoria.

SALARY: $A30,153 per annum (plus at present a non-superannuable clinical loading of $A2,500 per annum).

Further information about the above position, including details of application procedure, superannuation, travel and removal expenses, housing assistance and conditions of appointment, is available from the Registrar. All correspondence (marked "Confidential") should be addressed to the Registrar, The University of Melbourne, Parkville, Victoria 3052, Australia.

Applications close on 30 October, 1976.

IN MONILIASIS
BETADINE® Microbicides Vaginitis Regimen

Full Prescribing Information
BETADINE® Vaginal Gel
(povidone-iodine)

BETADINE Vaginal Gel (povidone-iodine) makes available elemental iodine in a form that maintains iodine's microbicidal activity, yet is virtually nonirritating, nontoxic and is nonstaining to skin and natural fabrics.

- Kills trichomonas, monilia, and other iodine-susceptible vaginal organisms responsible for specific and nonspecific vaginal infections.
- Active in the presence of blood, pus, or vaginal secretions.
- Virtually nonirritating to vaginal mucosa.
- Nonstaining to skin, linen or clothing of natural fabrics; color can be washed off with water.

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

Recommended regimen
In the office, swab the cervix and vulvovaginal area with BETADINE Solution.

Prescribe BETADINE Vaginal Gel (povidone-iodine) as follows: Insert one (1) applicatorful each night, followed the next morning by BETADINE Douche in its therapeutic concentration (2 tablespoonfuls to a quart of lukewarm water).

This regimen is to be followed through the entire menstrual cycle, including the days of menses. If further therapy is warranted, the regimen should be continued through the next two cycles. The patient may be instructed to return for an office visit following two weeks of therapy.

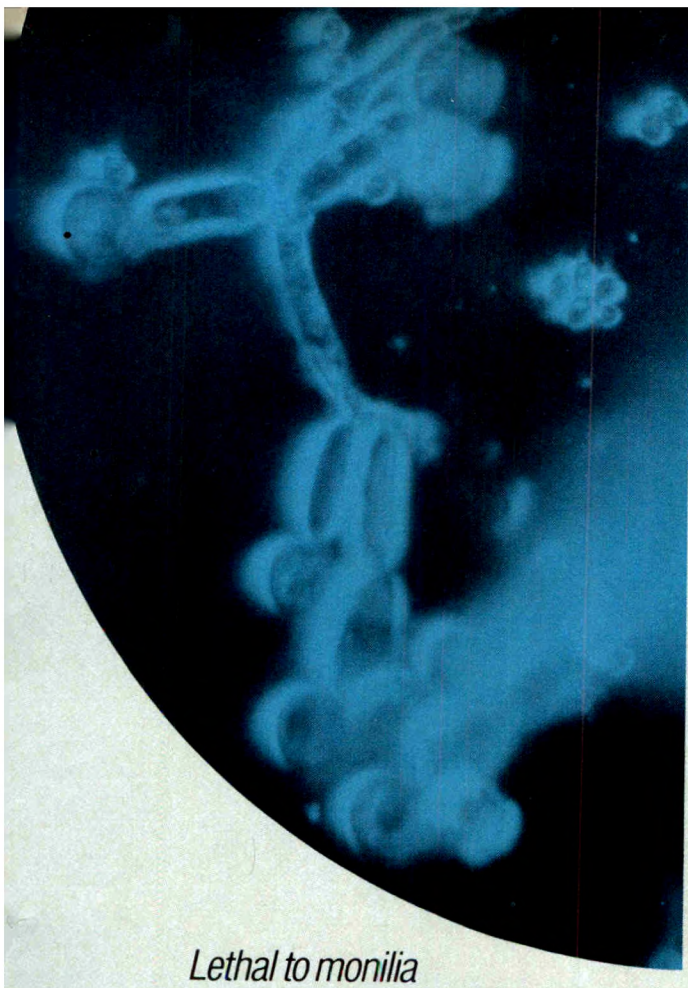
Precaution
If irritation, redness or swelling develop, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

Recommended dosage
One applicatorful (5 Gm.). Each five grams (one applicatorful) is equivalent to fifty milligrams of available iodine.

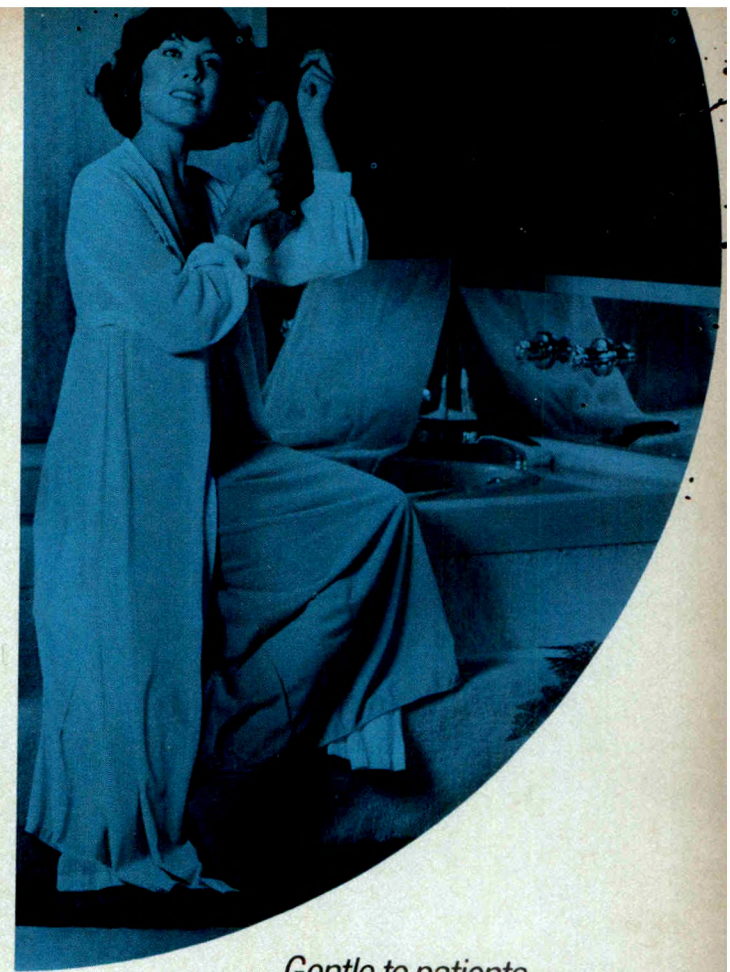
Supplied
18 Gm. and 3 oz. tubes with applicator.
Only on prescription.

Purdue Frederick

©COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A8201 171276



Lethal to monilia



Gentle to patients

IN MONILIASIS

BETADINE® Microbicides Vaginitis Regimen

High cure rate... rapid symptomatic relief

High cure rate is achieved in monilial vaginitis with the topical regimen employing BETADINE Microbicides:

BETADINE® SOLUTION
BETADINE® VAGINAL GEL*
(povidone-iodine)
BETADINE® DOUCHE

Easy-to-follow regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution which is promptly and decisively microbicidal. Prescribe BETADINE Vaginal Gel (povidone-iodine), one applicatorful of which is to be inserted each night, followed the next morning by BETADINE Douche in therapeutic concentration —2 tablespoonfuls to a quart of lukewarm water.

After 2 weeks

The patient returns for an office visit after two weeks of therapy. In more resistant cases, the regimen may have to be continued through 1 or 2 cycles. BETADINE Microbicides are virtually nonirritating to vaginal mucosa and do not stain skin and natural fabrics.

Lethal to other vaginal pathogens too

The broad-spectrum microbicidal action of BETADINE Microbicides kills not only monilia, but also *Trichomonas* and *Hemophilus vaginalis*.

Unlike exclusively antimonilial agents, the BETADINE MICROBICIDES VAGINITIS REGIMEN is not contraindicated when *Trichomonas* or *H. vaginalis* is present.

BETADINE Microbicides kill both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts. Their microbicidal action is maintained in the presence of blood, serum, and vaginal secretions.

*BETADINE Vaginal Gel (povidone-iodine) has been evaluated as possibly effective for use in the management of *Trichomonas vaginalis* vaginitis, monilial vaginitis and nonspecific vaginitis.

Purdue Frederick

See adjoining page for full prescribing information. A8335 178376

NEW Natafort®

COMPREHENSIVE PRENATAL VITAMIN FORMULA WITH MINERALS FROM PARKE-DAVIS

NATAFORT is a new, high-potency vitamin preparation with minerals, with special emphasis on the support *you* know is important for your pregnant patients.

- ■ *antianemia factors: iron and folic acid*
- ■ *calcium, 350 mg; and vitamin C*
- ☐ B-complex vitamins: niacinamide, vitamins B_1, B_2, B_6, and B_{12}
- ☐ other vitamins and minerals to help you support your patients' nutritional needs during pregnancy

Prescribe just one NATAFORT Tablet daily.



Each Natafort Tablet represents:

Vitamin A (acetate) (1.8 mg)	6,000 IU*
Vitamin D (ergocalciferol) (10 mcg)	400 IU
Vitamin C (ascorbic acid)	100 mg
Vitamin B_1 (thiamine mononitrate)	3 mg
Vitamin B_2 (riboflavin)	2 mg
Vitamin B_6 (pyridoxine hydrochloride)	15 mg
Vitamin B_{12} (cyanocobalamin) crystalline	5 mcg
Folic Acid†	1 mg
Nicotinamide (niacinamide)	15 mg
Vitamin E (*dl*-alpha tocopheryl acetate) (30 mg)	30 IU
Calcium (as calcium carbonate)	350 mg
Magnesium (as magnesium oxide)	1.7 mg
Iodine (as potassium iodide)	0.15 mg
Iron (as ferrous fumarate)	65 mg

Usual dose: One tablet daily

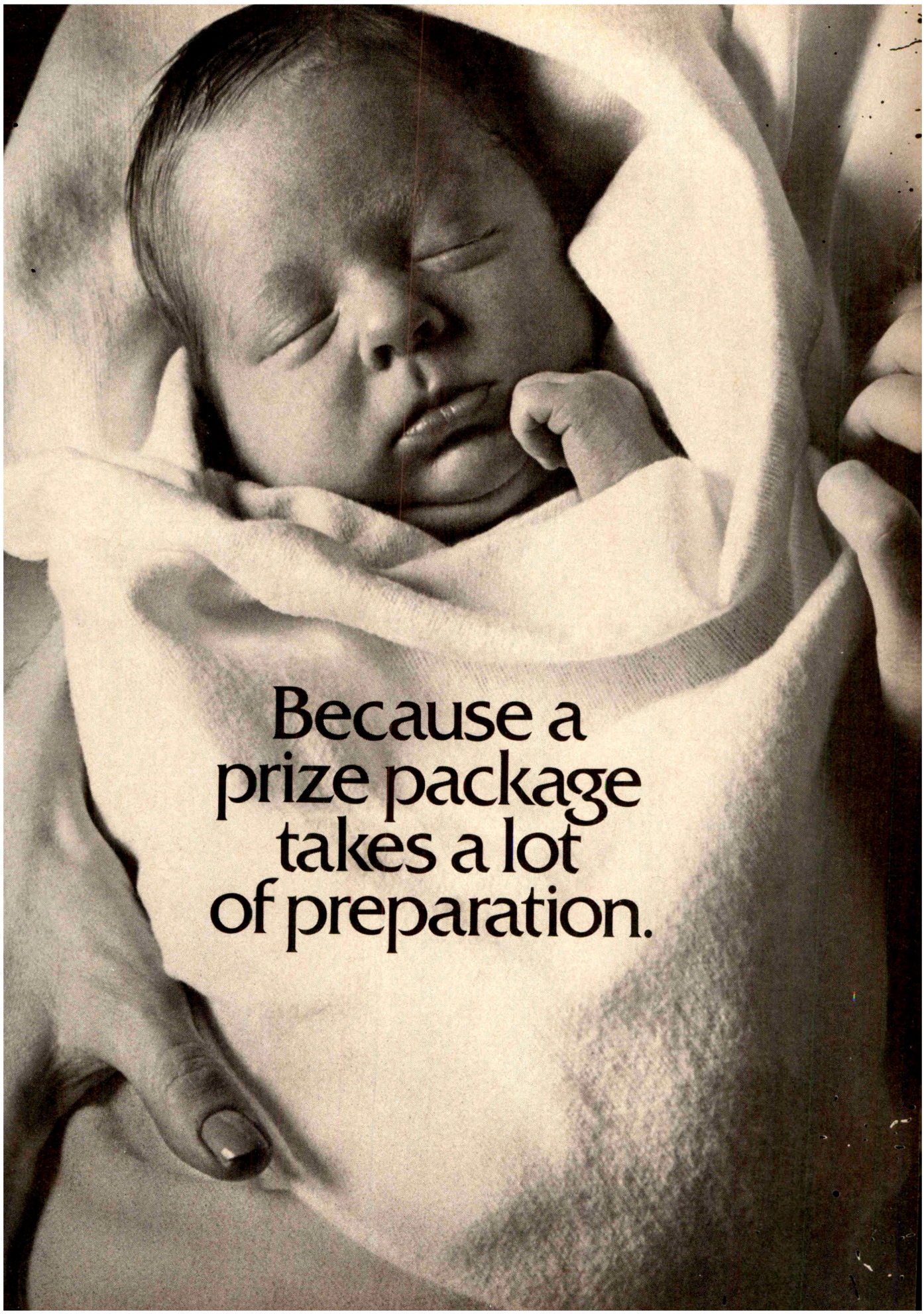
*IU=International Units

†CAUTION—Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.

PARKE-DAVIS

PARKE, DAVIS & COMPANY
Detroit, Michigan 48232

PD-JA-1955-1-P (5-76)


Because a
prize package
takes a lot
of preparation.

INDEX TO ADVERTISERS

Ames Company
N-Uristix ---------- 56, 57

Ayerst Laboratories
Dermoplast ---------- Fourth Cover
Premarin Vaginal Cream ---------- 44, 45

Breon Laboratories Inc.
Fergon ---------- 58

Burroughs Wellcome Co.
Empirin Compound with Codeine No. 3 ---------- 4

Carnation Company
Instant Milk ---------- 10

Elscint Inc.
Fetal Lung Maturity Analyzer ---------- 35

Fondation De Recherche En Hormonologie
Symposium ---------- 37

Hamot Medical Center
Classified ---------- 60

Harvard University
Classified ---------- 60

Imex Medical Systems, Inc.
Pocket-Dop ---------- 36

Mead Johnson Laboratories
Ovcon ---------- 31, 32, 33, 34

Merrell-National Laboratories
AVC ---------- 8

Ortho Pharmaceutical Corporation
Dienestrol ---------- 50, 51
Ortho-Novum 1/50 ---------- 46, 47, 48

Parke, Davis & Company
Loestrin 1/20 ---------- 14, 15, 16
Natafort ---------- 28, 29

Purdue Frederick Company, The
Betadine Microbicides ---------- 12
Betadine Perineal Wash ---------- 38
Betadine Vaginitis Regimen ---------- 26, 27
Senokot ---------- 53, 54, 55

R.J. Reynolds Industries, Inc.
Classified ---------- 1

Roche Laboratories
Gantanol ---------- 18, 19, 20

Roerig, A Division of Pfizer Pharmaceuticals
Geopen ---------- 42, 43

Schmid Laboratories, Inc.
Saf-T-Coil ---------- 52

Searle & Co., G.D.
Flagyl ---------- 60, Third Cover

Sierra Vista Community Hospital
Classified ---------- 26

Sonicaid, Inc.
Fetal Heart Detectors ---------- 1

Stryker Corporation
Ltd+1 OB Bed ---------- 25

Stuart Pharmaceuticals, Division of ICI United States Inc.
Prenatals ---------- 41

Syntex Laboratories, Inc.
Service Program ---------- 39, 40
Vagitrol ---------- Second Cover, 1

University of Melbourne
Classified ---------- 26

Wiley & Sons, Inc., John
Books ---------- 59

Wyeth Laboratories
Lo/Ovral ---------- 22, 23, 24
Ovral ---------- 49

Xerox Corporation
Xeroradiography ---------- 2, 3

Zeiss, Inc., Carl
Colposcopes ---------- 6

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Mead Johnson announces

OVCON®

ne name to remember
in low-dose oral contraceptives

two doses
from which to select

LOW DOSE

LOWER DOSE

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

OVCON®-35*

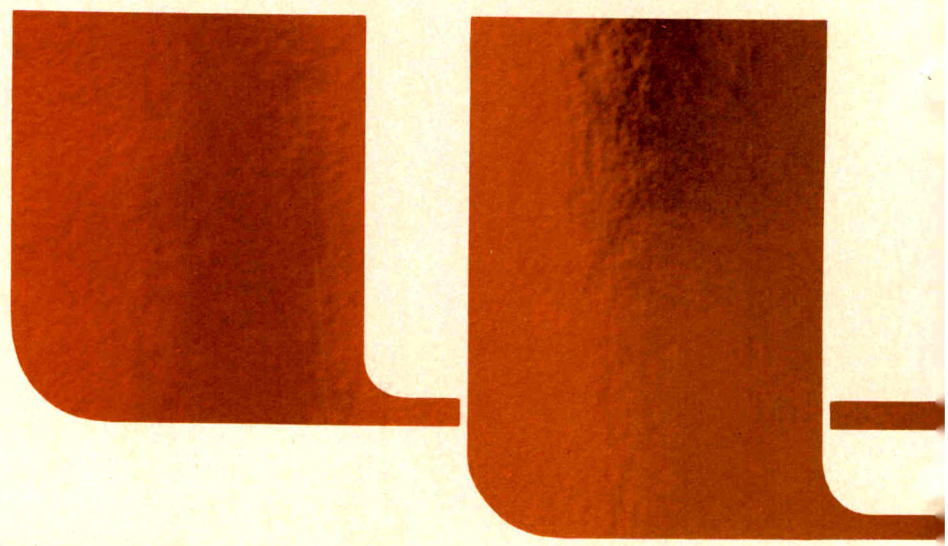
21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

For Brief Summary, please see last page of this advertisement.

One name to remember in combination oral contraceptive effectiveness...

OVCON®

two doses from which to select



providing...

- **effective low-dose contraceptive protection***
- **low incidence of common side effects†**
- **acceptable cycle control†**
- **in-depth clinical studies in widely different populations**

Mead Johnson LABORATORIES

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

tested in 1,028 women for 9,558 cycles[1]

Although these women represented a wide range of socioeconomic groups with inherent differences in motivation, pregnancy rate (Pearl's formula) was 0.13 pregnancies per 100 woman years due to method failure and 0.75 pregnancies per 100 woman years due to patient failure. This results in a use-effectiveness of 0.88 pregnancies per 100 woman years.

Few women—2.7%—discontinued therapy for cycle-related reasons . . . and these were not necessarily spotting or breakthrough bleeding, but included amenorrhea and what women considered bleeding too little or too much. There was a discontinuation rate of 10.8% for all other on-therapy conditions, which, however, were not necessarily caused by Ovcon-50.

OVCON®-35*

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

tested in 1,861 women for 20,230 cycles[1]

In these women, with a wide range of backgrounds and motivations, there was effective control of conception. Pregnancy rate (Pearl's formula) due to method failure was 0.41 pregnancies per 100 woman years, and 0.95 pregnancies per 100 woman years were due to patient failure. This results in a use-effectiveness of 1.36 pregnancies per 100 woman years.

There was a higher discontinuation rate —11.6%—for cycle-related reasons with Ovcon-35 than with Ovcon-50, but, again, reasons included any spotting as well as amenorrhea and bleeding too much, too little, or irregularly. On the other hand, the discontinuation rate for all other on-therapy conditions, which were not necessarily related to Ovcon-35, was quite low—7.1%.

1. Data on file, Mead Johnson Laboratories.

OVCON-50 and OVCON-35* offer the advantages of effective low-dose protection and of uninterrupted regimens— 21 active tablets and 7 inert tablets

For Brief Summary, please see following page.

*The effectiveness of Ovcon-35 is somewhat lower than higher-dose combination products.

†See "Special Note" section of prescribing information on last page of this advertisement.

two dosages from which to select

LOW DOSE
OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets.

LOWER DOSE
OVCON®-35

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. The effectiveness of OVCON-35 is somewhat lower than higher-dose combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons due to menstrual disorders and irregularities appears to be higher for OVCON-35 than that observed with higher-dose combination products. An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Oral contraception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen dependent neoplasia; undiagnosed abnormal genital bleeding; known or suspected pregnancy.

Warnings: If signs of thrombotic and thromboembolic disorders (thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis) occur or are suspected, use of the drug should be discontinued immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug use was discontinued and not enhanced by long-term use.[1-10]) If gradual or sudden, partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11-13] Safety of use in pregnancy has not been established, therefore pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant cannot be determined at this time. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in short-term as well as long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

Precautions: A thorough history and physical examination of breasts and pelvic organs should include Papanicolaou smears. (Estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after the drug has been withdrawn for two months. Under the influence of these drugs, pre-existing uterine fibromyomata may increase in size. Some conditions (epilepsy, migraine, asthma, cardiac or renal dysfunction) might be influenced by fluid retention. Observe carefully for such. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged OVCON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. Diabetic patients should be carefully observed while receiving such therapy. The age of the patient constitutes no absolute limiting factor, although these drugs may mask the onset of the climacteric. The pathologist should be advised of OVCON therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. If cholestatic jaundice occurs, OVCON should be discontinued. This condition is more likely to occur in patients with a history of cholestatic jaundice of pregnancy.

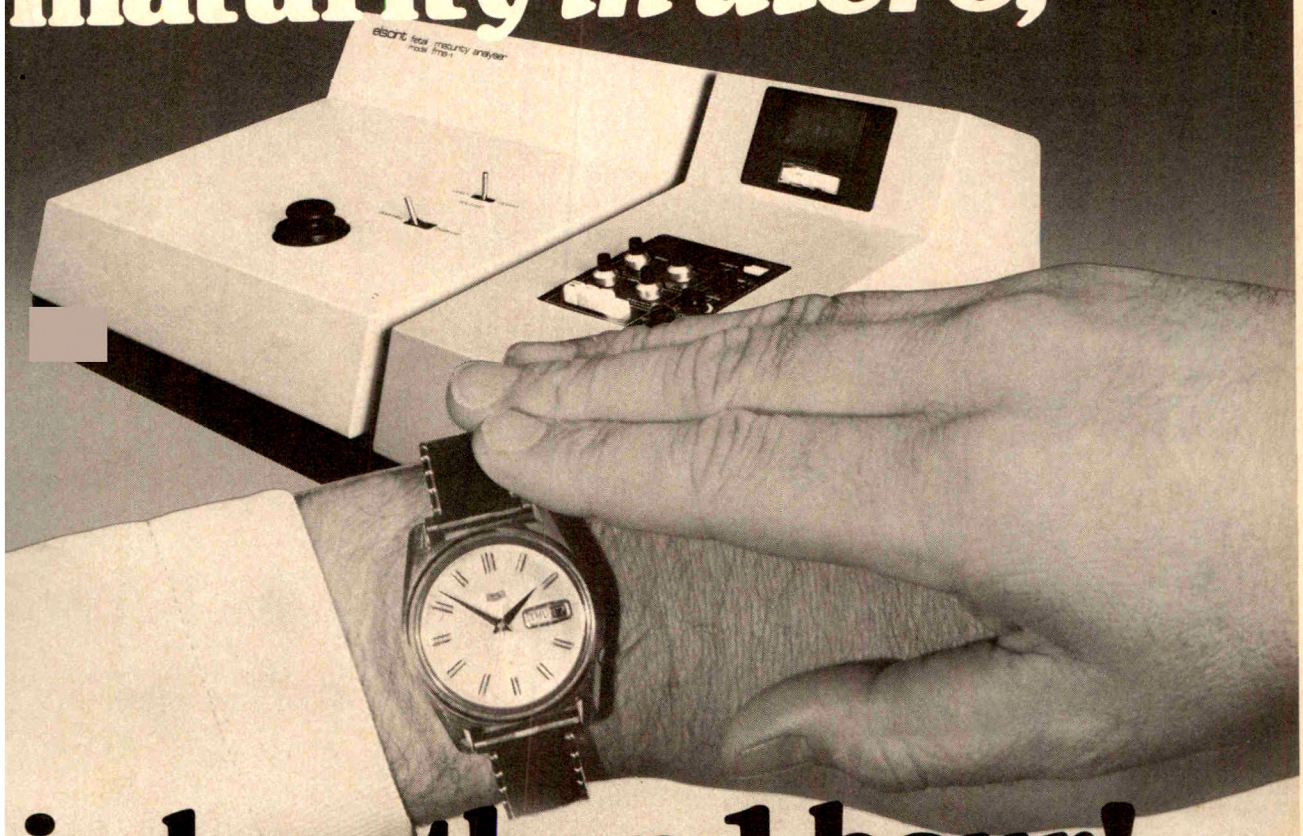
Adverse Reactions Observed in Patients Receiving Oral Contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage and gall bladder disease. Suggestive evidence, neither confirmed nor refuted, between use and: neuro-ocular lesions (retinal thrombosis and optic neuritis) and hepatic lesions with or without intra-abdominal bleeding. Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps and bloating), breakthrough bleeding, change in menstrual flow, spotting, amenorrhea during and after treatment, breast changes (tenderness, enlargement and secretion), mental depression, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals, edema, chloasma or melasma (which may persist), cholestatic jaundice, migraine, rash (allergic). Reported association with use, neither confirmed nor refuted: anovulation post treatment; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; intolerance to contact lenses; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; vaginitis. *May Alter Laboratory Results in:* Hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X, decrease in anti-thrombin III and an increase in norepinephrine-induced platelet aggregability), thyroid function (increase in PBI, and butanol extractable protein bound iodine and decrease in T_3 uptake values), metyrapone test, pregnanediol determination.

References: (1) Royal College of General Practitioners: Oral contraception and thromboembolic disease. J. Coll. Gen. Pract. *13*:267-279, 1967. (2) Inman, W.H.W. and Vessey, M. P. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women in child-bearing age. Brit. Med. J. *2*:193-199, 1968. (3) Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease: A further report. Brit. Med. J. *2*:651-657, 1969. (4) Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. Thromboembolism and oral contraceptives: An epidemiologic case-control study. Amer. J. Epidem. *90*:365-380, 1969. (5) Oral contraception and increased risk of cerebral ischemia or thrombosis. New Eng. J. Med. *288* (17):871-877, 1973. (6) Oral contraceptives and stroke in young women. JAMA *231*(7):718-722, 1975. (7) Boston Collaborative Drug Surveillance Programme. Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumours. Lancet *1*:1399-1404, 1973. (8) Oral Contraceptives and Health. A summary of an interim report from the oral contraception study of the Royal College of General Practitioners, May, 1974. (9) Vessey, M. P., Doll, R., Fairbairn, A. S., and Glober, G. Post-operative thromboembolism and the use of oral contraceptives. Brit. Med. J. *3*:123-126, 1970. (10) Greene, G. R. and Sartwell, P. E. Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am. J. Public Health *62*:680-685, 1972. (11) Nora, A. H. and Nora, J. J. A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch. Envir. Health *30*:17-21, 1975. (12) Janerich, D. T., Piper, J. M., and Glebatis, D. M. Oral contraceptives and congenital limb-reduction defects. New Eng. J. Med. *291*(14):697-700, 1974. (13) Carr, D. H. Cytogenetics and malformations in abortions. Fed. Proc. *30*:102-103, 1971.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 754095

Now...accurately determine fetal lung maturity *in utero*,



in less than 1 hour!

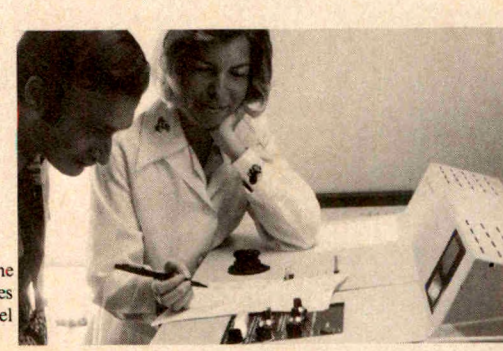
When an unborn life is in the balance, a fast precise lab test can make the crucial difference. The new Elscint FELMA (Fetal Lung Maturity Analyzer) can give you this important edge, quickly and accurately.

Designed to deliver fast, precise results in less than one hour, the FELMA is a highly sophisticated, clinically-proven * device requiring a simple clinical procedure — the extraction of as little as 0.5 ml. of amniotic fluid.

Because it's based on electro-optical principles, you get reliable, reproducible results each time Such accuracy will make easier those critical decisions about emergency steps which may be necessary.

The FELMA is a space-saver, too, requiring as little space as a desk. No special laboratory equipment is required; all that's needed to run the tests are a centrifuge and a small heating bath.

Call or write today for detailed information about this significant new development.



Uncomplicated, no-delay operation!

Faster, simpler and more accurate than the L/S ratio test.

- Centrifuge amniotic fluid (10 min.).
- Add reagent (available from Elscint.).
- Incubate (20 min.).
- Cool (10 min.) at room temperature.
- Readout results on digital LED display.

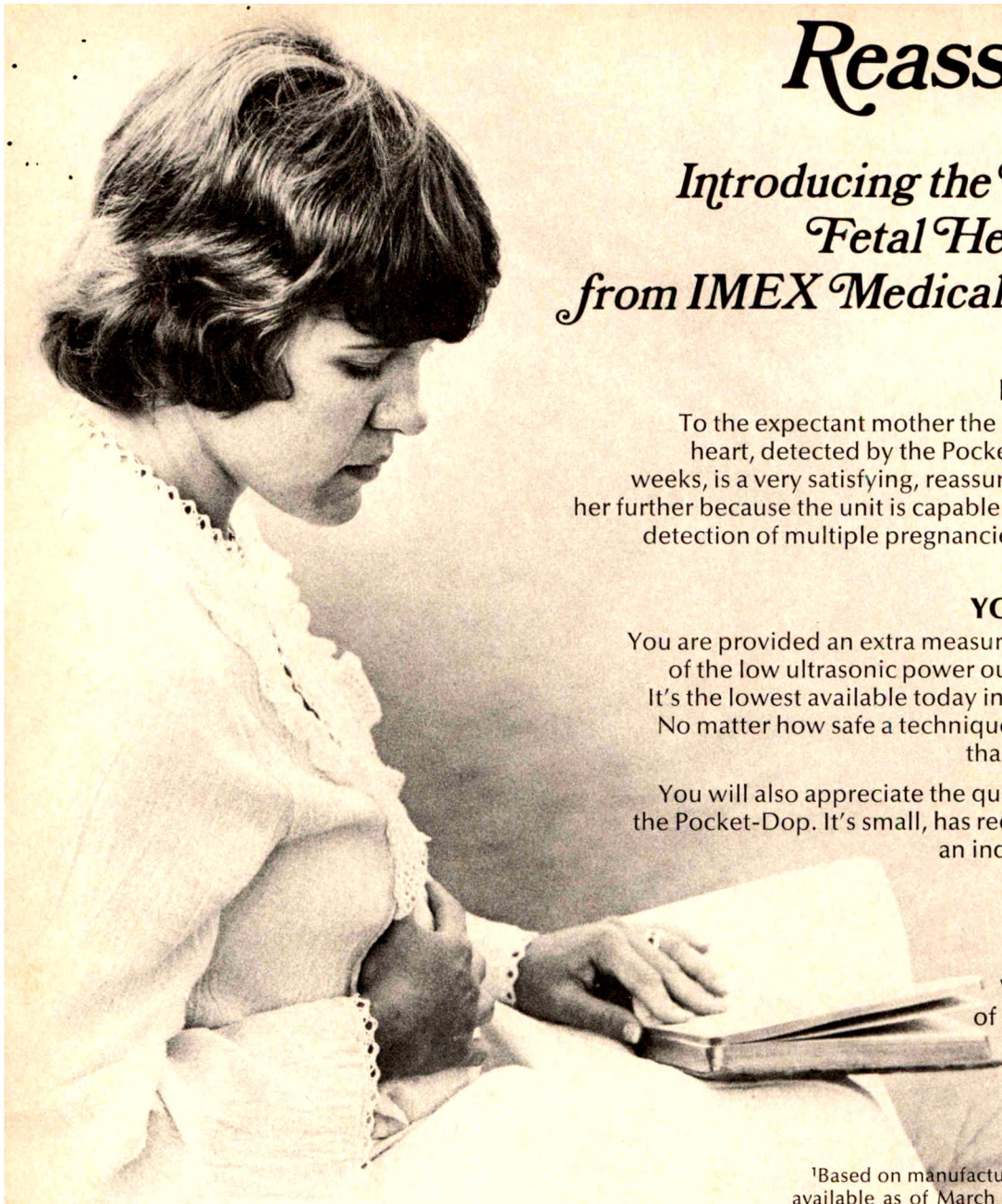
*Tested in the United States and Israel

elscint inc.

Where quality counts . . . count on Elscint.

P.O. Box 832; Hackensack, N.J. 07602 Tel. (201) 487-5885.

In United Kingdom: Elscint GB, 5 Priestley Way, Crawley Sussex RH102DW. Telephone: Crawley (0293) 21285/6/7. In France: Elscint S.A.R.L, 11 Rue Edouard-Lefebvre 78000 Versailles, Telephone: 950-2767. In Germany: Elscint GMBH, Freudenbergstrasse 27, 62 Wiesbaden-Schierstein, Telephone: (06121) 2786. In other countries: Write to Elscint Ltd., P.O. Box 5258, Haifa, Israel for the office in your country.



Reassurance

Introducing the Pocket-Dop Fetal Heart Detector from IMEX Medical Systems, Inc.

HER REASSURANCE

To the expectant mother the rapid rhythm of the fetal heart, detected by the Pocket-Dop as early as 8 to 12 weeks, is a very satisfying, reassuring sound. You can help her further because the unit is capable of placenta localization, detection of multiple pregnancies and labor monitoring.

YOUR REASSURANCE

You are provided an extra measure of confidence because of the low ultrasonic power output of the Pocket-Dop. It's the lowest available today in this type of instrument.[1] No matter how safe a technique is why use more power than is clinically necessary?

You will also appreciate the quality and convenience of the Pocket-Dop. It's small, has rechargeable batteries and an indicator light, can be used with built-in speaker or private earphone and includes a probe with a nontangle, coiled cord. Why not take advantage of our no-risk offer below?

[1]Based on manufacturers' published specifications available as of March 15, 1976. Actual Pocket-Dop output less than 0.5mw/cm². Details on request.



Please send me.....IMEX Pocket-Dop units including manual, coupling gel, recharger and earphone @ $369/ea. Also included is a 33⅓ rpm "soundsheet" recording of doppler sounds made with the cooperation of Dr. Kenneth Gottesfeld, Denver, CO.

Name..... Phone.....

Address .....

City..... State..... Zip.....

Signature .....

I understand if I am not completely satisfied with the Pocket-Dop I can return the instrument within three weeks of delivery and my complete purchase price will be promptly refunded to me.

DIAGNOSTIC USES OF ULTRASOUND
THIS $30 BOOK YOURS AT NO ADDITIONAL CHARGE. By including payment now we will send you at no extra cost *Diagnostic Uses of Ultrasound* by Goldberg, et al. Chapters on ultrasound in gynecology, obstetrics, doppler uses, ultrasound principles.

☐ Check enclosed. ☐ Master Charge ☐ BankAmericard

☐ Please bill me.

Please charge:

Acct. #..... Exp. Date.....

Master Charge Interbank #.....
(4 nos. over your name)

Mail to:

IMEX

imex medical systems, inc.
9305 blue mountain dr.
golden, colorado 80401
(303) 642-7316

FETUS, PLACENTA, AND NEWBORN

Antepartum fetal heart rate and uterine activity studies

I. Preliminary report of accelerations and the oxytocin challenge test

H. E. FOX, M.D.
M. STEINBRECHER, B.S.
B. RIPTON, B.S.N.
Rochester, New York

A series of 344 antepartum fetal heart rate studies in 209 high-risk patients is described. The importance of evaluation of accelerations of the fetal heart rate as well as periodic decelerations associated with uterine activity is demonstrated. Our data suggest that the absence of accelerations of the fetal heart rate during the recording period may be associated with increased perinatal morbidity. Late decelerations may occur in the same recording session as accelerations of the fetal heart rate. The association of late decelerations of the fetal heart rate with no accelerations during the recording session is highly suggestive of increased perinatal morbidity. In high-risk patients, accelerations of the fetal heart rate and no late decelerations with uterine activity are a reassuring finding, with 91 per cent of patients showing no increased perinatal morbidity.

CONTINUOUS MONITORING of the fetal heart rate and uterine activity has provided information which may help the obstetrician make a judgment regarding fetal status during labor. Periodic decelerations of the fetal heart rate which are believed to be related to a decrease in fetal oxygenation secondary to uteroplacental insufficiency have been defined.[1] The intrapartum association of late decelerations of the fetal heart rate and increased risk for low Apgar score and metabolic acidosis during labor and at delivery has been well documented.[2]

In the past few years, major emphasis has been placed on antepartum fetal heart rate monitoring as a method of assessment of fetal-placental function. A variety of "stresses" have been studied including maternal exercise,[3] regulation of maternal inspired oxygen and carbon dioxide, and oxytocin stimulation. Results of the oxytocin challenge test[4-7] have indicated that antepartum fetal monitoring may permit the physician to avoid unnecessary intervention when signs of uteroplacental insufficiency are absent.[7]

Although decelerations of the fetal heart rate have received most attention, the occurrence of accelerations of the fetal heart rate also have been noted. It is believed that accelerations of the fetal heart rate are reassuring and indicate a general state of fetal well-being.[8] This report presents the results of a study of

From the Perinatal Unit, Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry.

Supported in part by The National Foundation–March of Dimes Medical Service Grant.

Received for publication November 20, 1975.

Revised March 4, 1976.

Accepted March 19, 1976.

Reprint requests: Dr. H. E. Fox, Department of Obstetrics and Gynecology, University of Rochester, 601 Elmwood Ave., Rochester, New York 14642.

Table I. Primary diagnosis

Primary diagnosis	*No. of patients*
Diabetes	
A	25
B or >	24
Toxemia	29
Chronic hypertension	23
Suspected postmaturity	36
Renal disease	17
Intrauterine growth retardation*	12
Previous stillborn infant	8
Decreased fetal movement	8
Fetal heart rate irregularity	10
Rh(-)-sensitized*	7
Other	10

*One fetal death.

Table II. Causes of inadequate studies

Cause	*No. of studies*
Recording difficulty (fetal or maternal movement, arrhythmia, anterior placenta)	40
Technique error (discontinued study prior to adequate uterine activity)	25
Potential fetal risk (hyperstimulation, supine hypotension)	10
Total	75

fetal heart rate accelerations and periodic late decelerations associated with spontaneous or induced uterine activity with regard to perinatal morbidity and death.

Material and methods

High-risk population. Patients were selected from the high-risk obstetric clinic at the University of Rochester Medical Center and from private physician referrals. Table I indicates the primary diagnoses of the study population. A total of 344 adequate studies were obtained in 209 patients. The age range was 13 to 42 years with parities from 0 to 8. Eight patients had five studies performed. The earliest gestational age studied was 32 weeks. No patient went into labor prematurely within 72 hours of oxytocin administration for uterine activity stimulation. Each patient gave written informed consent prior to each study.

Technique. Studies were performed by a special project nurse. The patient was placed on a bed in the semi-Fowler position with the head elevated 30 degrees. Blood pressure was measured at 15 to 20 minute intervals to be certain that unrecognized supine hypotension and potential compromised uterine blood flow did not occur. A continuous record (paper speed 3 cm. per minute) of fetal heart rate (40 to 220 beats per minute) and an indication of uterine activity were obtained with a fetal monitor.* Late in the study, an external fetal electrocardiographic system† was utilized as adapted to the Roche fetal monitor. An intravenous infusion of 5 per cent dextrose and water was begun after a 15 minute base-line recording period if uterine activity did not show three firm contractions in 10 minutes. In diabetic patients, plain lactated Ringer's solution was utilized. Oxytocin was delivered by a volume-controlled infusion pump‡ starting at 0.5 mU. per minute. The infusion rate was increased every 15 minutes until three clinically firm contractions (by palpation) occurred in a 10 minute period or until late decelerations became evident.

Study result classifications. Following an adequate study, the record was reviewed and classified in one of four groups: (1) Positive study—late decelerations occur with each contraction during the acceptable 10 minute period. Subclassification indicating the presence or absence of accelerations of the fetal heart rate is noted. (2) Inadequate study—the study reveals recording difficulties, technique error, or potential fetal risk due to hyperstimulation or supine hypotension. Whenever possible, a repeat study was performed the next day. (3) Negative study—an adequate study period is achieved with no late-deceleration patterns. The presence or absence of fetal heart rate accelerations is noted. (4) Equivocal study—inconsistent late decelerations occur during the study period. The presence or absence of accelerations of the fetal heart rate is noted.

Assessment of perinatal morbidity. In order to indicate the value of the antepartum fetal heart rate/uterine activity studies, criteria for increased perinatal morbidity were established as follows: (1) a low Apgar score (one minute, less than or equal to 4, or five minute, less than or equal to 6) not associated with difficult delivery; (2) biochemical evidence of fetal-placental failure as indicated by a 35 per cent fall in total urinary estrogen excretion compared to a mean of the previous three collections; (3) fetal distress by electronic or biochemical monitoring techniques in labor; (4) increased neonatal morbidity. Fetal distress in labor is defined as the occurrence of late decelerations or prolonged decelerations of the fetal heart rate requiring obstetric intervention or biochemical evidence (by scalp sampling) of acidosis. Neonatal mor-

*Model 2102, Roche Medical Electronics Div., Hoffmann-La Roche Inc., Brick Yard Rd., Cranbury, New Jersey 08512.

†Model 8023A, Hewlett-Packard Co., 1501 Page Mill Rd., Palo Alto, California 94304.

‡No. 922, IMED.

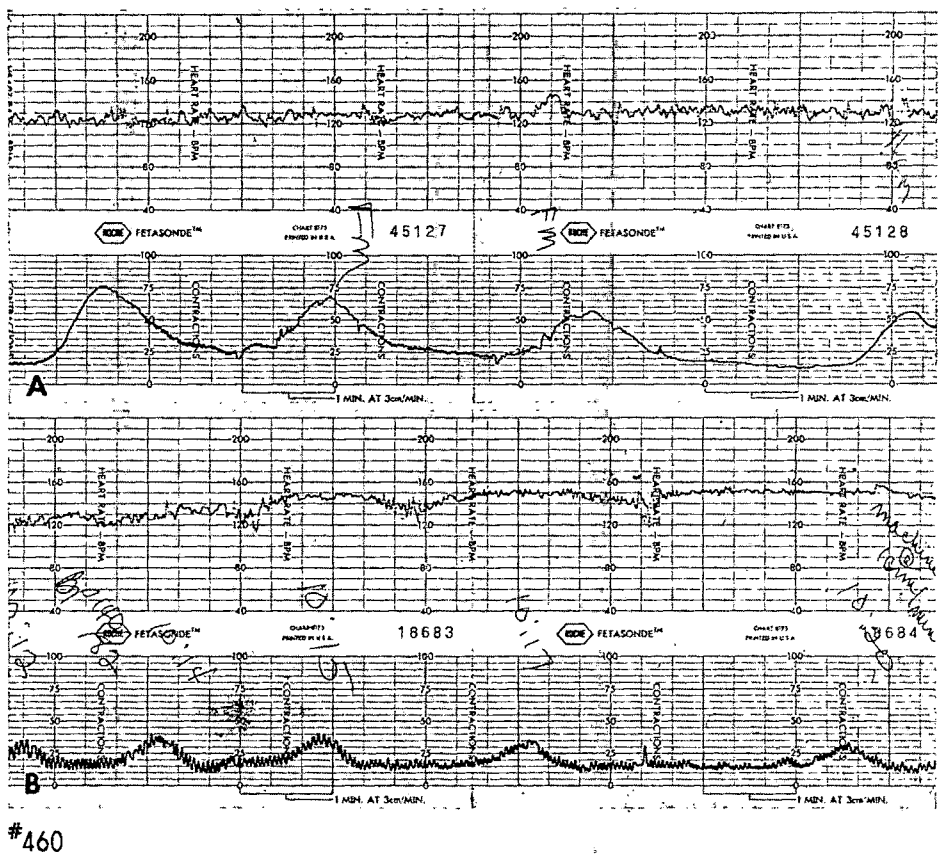


Fig. 1. *A,* Negative study with accelerations in a patient with chronic hypertension at 38 weeks. *B,* Positive study in same patient one week later. Accelerations were noted in base-line recording period. Total urinary estrogens reported the same day had fallen 38 per cent.

bidity is defined as early depression or metabolic acidosis of the newborn infant, documented postmaturity, or growth retardation.

One hundred and eighty patients had adequate data regarding perinatal morbidity and a study performed within one week of delivery.

Results

Three hundred and forty-four adequate studies were obtained from a total of 419 attempts in 209 patients. The mean time for an adequate study period was 50 minutes with a standard deviation of 22 minutes. The mean oxytocin infusion rate to achieve an adequate study period was 8 mU. per minute with a range of 0 to 20 mU. per minute. In 23 studies, spontaneous uterine activity fulfilled criteria for a successful study period. Six of 11 patients studied immediately after amniocentesis fulfilled the uterine activity criteria without oxytocin augmentation.

Table II indicates the causes identified for the 75 inadequate studies in this series. In the 209 patients, the inadequate study rate on the initial attempt was 10 per cent. It was not possible to obtain an adequate study on the first repeat test in eight patients, indicating a repeat failure rate of 4 per cent. Six patients did not have a repeat study attempt.

A common reason for an inadequate study was the technique error of discontinuing the study before adequate uterine activity was achieved. In our series two fetal deaths occurred at three and seven days after inadequate studies which were not repeated.

Study result examples. A negative study period obtained from a patient at 38 weeks' gestation with chronic hypertension is shown in Fig. 1, *A*. Accelerations of the fetal heart rate are associated with fetal movement. Fig. 1, *B* shows a positive study period in the same patient at 39 weeks. Accelerations with fetal movement were seen in the base-line record. Total urinary estrogen results reported later the same day revealed a drop of 38 per cent from the mean of the previous three collections. Monitored labor induction by artificial rupture of the membranes and oxytocin

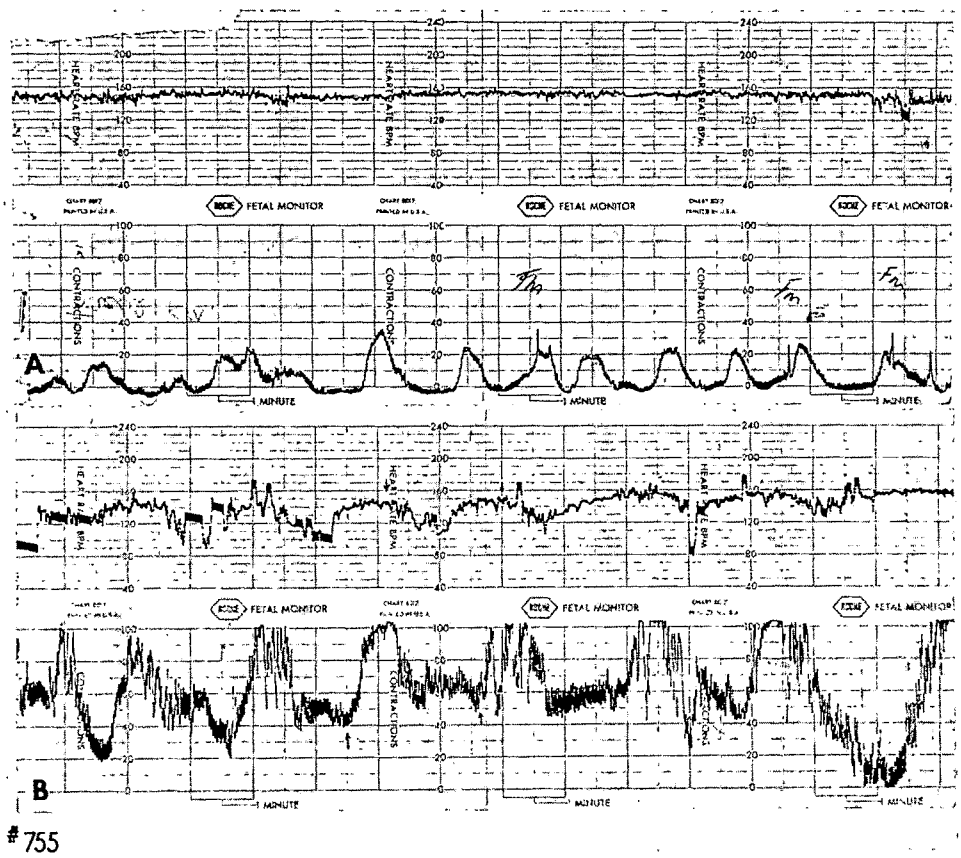


Fig. 2. *A,* Base-line fetal heart rate record without accelerations in a patient with Class C diabetes at 38 weeks. (Note: paper speed 2 cm. per minute.) *B,* Induced uterine activity led to a positive study. Trial of labor resulted in delivery by cesarean section of an SGA infant, Apgar score 2/4. (Note: paper speed 2 cm. per minute.)

augmentation resulted in vaginal delivery of an infant with an Apgar score of 7-8. Multiple placental infarcts were noted.

The base-line fetal heart rate record from a Class C diabetic patient with hypertension at 38 weeks is presented in Fig. 2, *A*. No accelerations were noted. When satisfactory uterine activity was achieved by oxytocin stimulation, a late-deceleration pattern developed, as is seen in Fig. 2, *B*. A trial of labor, initiated by artificial rupture of the membranes and oxytocin augmentation, was terminated by a cesarean section for fetal distress with the delivery of a small–for–gestational age (SGA) infant weighing 2,200 grams with an Apgar score of 2-4.

A positive study on a patient referred for postmaturity at 43 weeks' gestational age is shown in Fig. 3, *A*. No accelerations were noted. Attempted induction of labor by artificial rupture of the membranes and subsequent oxytocin augmentation resulted in a cesarean section for fetal distress based on the late decelerations which developed in labor and persisted after discontinuation of oxytocin (Fig. 3, *B*). At delivery the umbilical arterial pH was 7.12 and the venous pH was 7.25.

Fig. 4, *A* shows accelerations of the fetal heart rate recorded in the base-line period in a patient at 41 weeks with epilepsy and the nephrotic syndrome. Stimulation of adequate uterine activity reveals a positive study period (Fig. 4, *B*). This pregnancy was terminated within 24 hours with no indication of perinatal morbidity. At delivery, the umbilical arterial pH was 7.25 and the venous pH was 7.33. Supine hypotension had not occurred.

Two patients in this series experienced fetal death. One patient was Rh negative and sensitized with fetal death occurring at 33 weeks. The second patient had severe intrauterine growth retardation well documented by ultrasound and low total urinary estrogens. There was no satisfactory study period within seven days of death in either case. However, both had inadequate tests that were not repeated and showed no accelerations of the fetal heart rate. Fig. 5 presents the recording of the fetal heart rate in the patient ex-

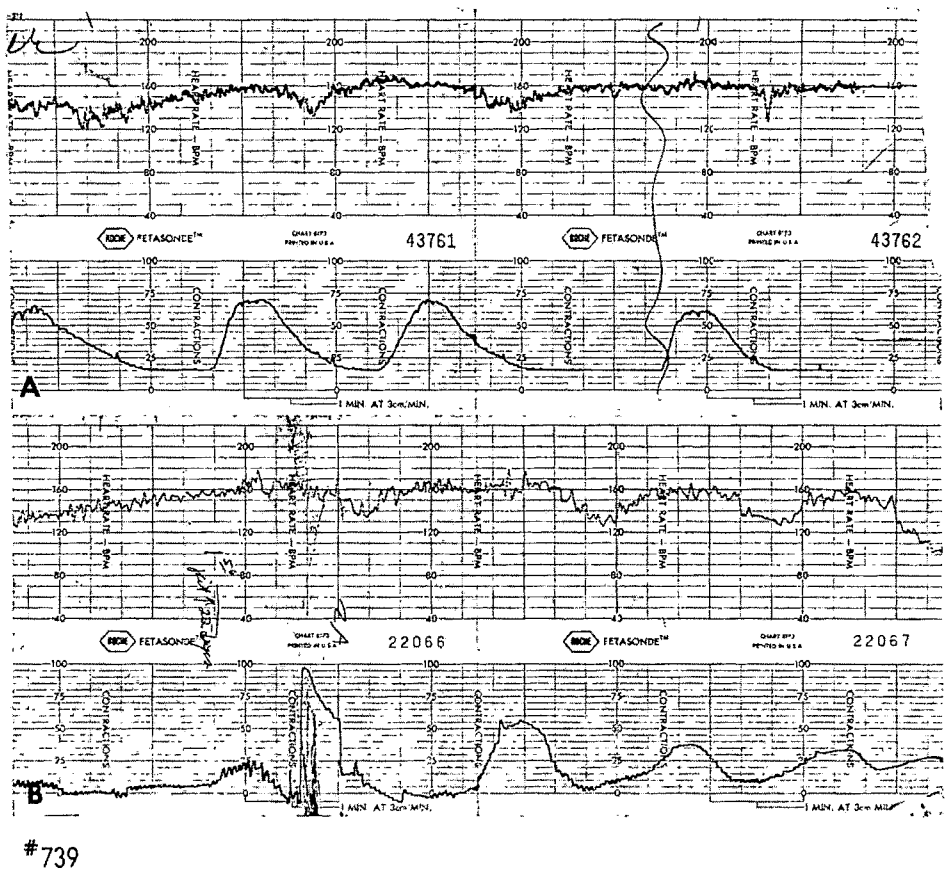


Fig. 3. *A*, Positive study without accelerations at 43 weeks. *B*, Late decelerations developed during trial of labor on the same day.

periencing fetal death at 38 weeks. The 90 minute record obtained two days prior to fetal death shows no accelerations.

Late decelerations may be recorded in response to spontaneous uterine activity. Fig. 6 is a record obtained from a patient with severe intrauterine growth retardation and chronic hypertension at 35 weeks' gestation. The recording was carried out at a community hospital and transmitted via a Xerographic Telecopier* to the Medical Center for consultation. No accelerations were noted, and consistent late decelerations occurred with mild spontaneous uterine activity. The patient was not hypotensive. A neonatal transport team was dispatched for the delivery by cesarean section of a 1,175 gram infant with an Apgar score of 2-9.

Negative studies. One hundred and sixty-three patients had negative studies within one week prior to delivery. One hundred per cent of the infants survived. Seventy-six per cent were considered to have a good fetal outcome with increased perinatal morbidity noted in the remaining 24 per cent. Eighteen patients had equivocal studies. Subsequently, 13 had negative studies and five had positive studies.

Positive studies. Seventeen patients with definable morbidity had positive studies with late decelerations occurring with each uterine contraction. The earliest positive study occurred in a patient with severe toxemia at 33 weeks' gestational age. Fourteen patients were delivered of their infants within 24 hours of the positive study. Survival was 100 per cent with increased perinatal morbidity in 59 per cent of the patients. Seven patients were delivered vaginally without signs of increased perinatal morbidity.

Perinatal morbidity groups. In review of the patients showing a positive study, three distinct groups were identified. Table III summarizes the three perinatal morbidity groups. Group 1 consists of all patients who had a positive study period (late decelerations with uterine activity) and who did not demonstrate increased perinatal morbidity. These patients (No. = 7) were all delivered vaginally, were monitored with no signs of fetal distress, and demonstrated no increased morbidity in the neonatal period.

*Model 400, Xerox Data Systems, 701 S. Aviation Blvd., El Segundo, California 90245.

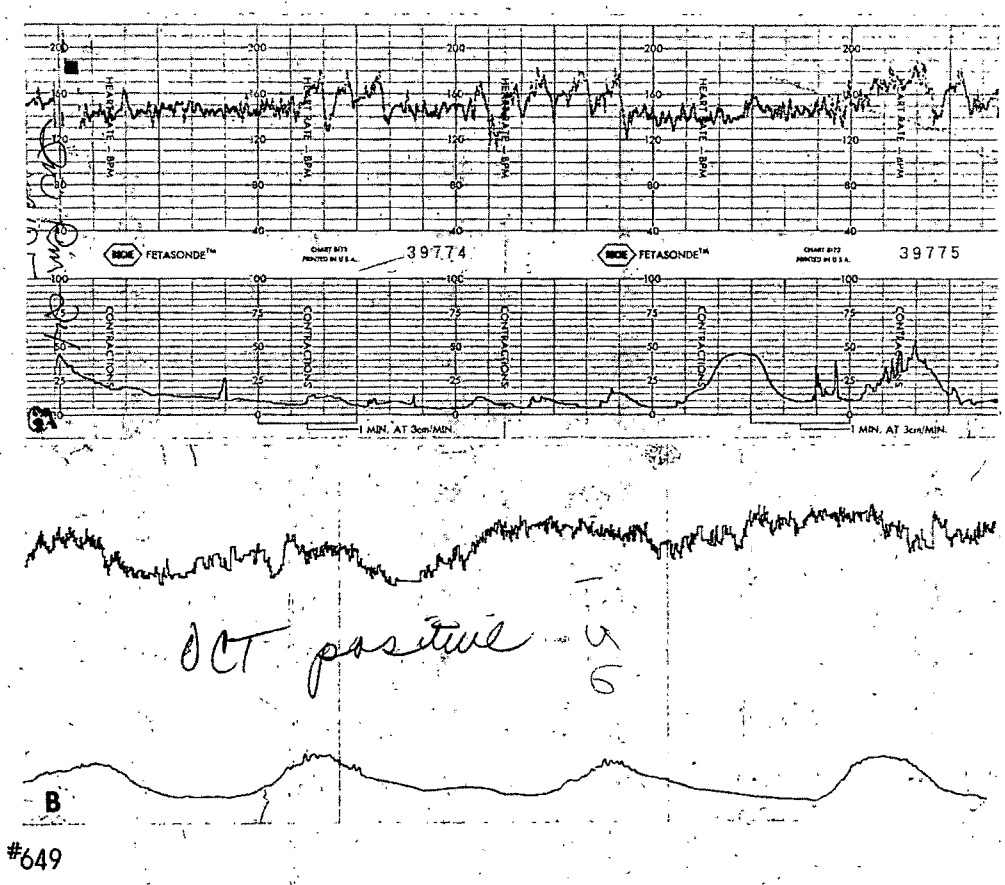


Fig. 4. *A*, Base-line fetal heart rate record demonstrates accelerations in a patient with the nephrotic syndrome at 41 weeks. *B*, Positive study period in the same patient. An infant with Apgar score 9/10 was delivered.

Table III. Perinatal morbidity groups

Group 1
Positive study without increase in perinatal morbidity
1. Vaginal delivery without fetal distress
2. No neonatal morbidity
Group 2
Positive study with increased perinatal morbidity
1. Low Apgar score
2. Neonatal morbidity
3. Biochemical evidence of fetal/placental failure
4. Fetal distress in labor
Group 3
Positive study unable to define perinatal morbidity
1. Cesarean section without labor
2. No neonatal morbidity

Table IV. Accelerations of fetal heart rate (215 patients*)

Results	*Present (148 patients)*	*Absent (67 patients)*
Survival	148 (100%)	65 (97%)
Good outcome	133 (90%)	36 (54%)
Over-all increased morbidity	15 (10%)	31 (46%)
Intrapartum fetal distress	5	14
Falling estriol	1	2
Low Apgar score	6	9
Neonatal morbidity	8	18*

*Includes two fetal deaths.

The second group (Group 2) includes patients with a positive study and increased perinatal morbidity. Eight of the 10 patients in this group had a monitored trial of labor ending in cesarean section delivery for fetal distress. Two had a marked fall in estriol levels (33 per cent or greater) and were delivered vaginally without evidence of fetal distress.

The third group (Group 3) is made up of five patients with positive studies who underwent cesarean section without labor because of previous cesarean section, breech presentation, or active genital herpes infection. No perinatal morbidity was seen in this group.

Diagnostic category and increased perinatal morbidity. Of the 10 patients with a positive study and increased perinatal morbidity, three were Class B or

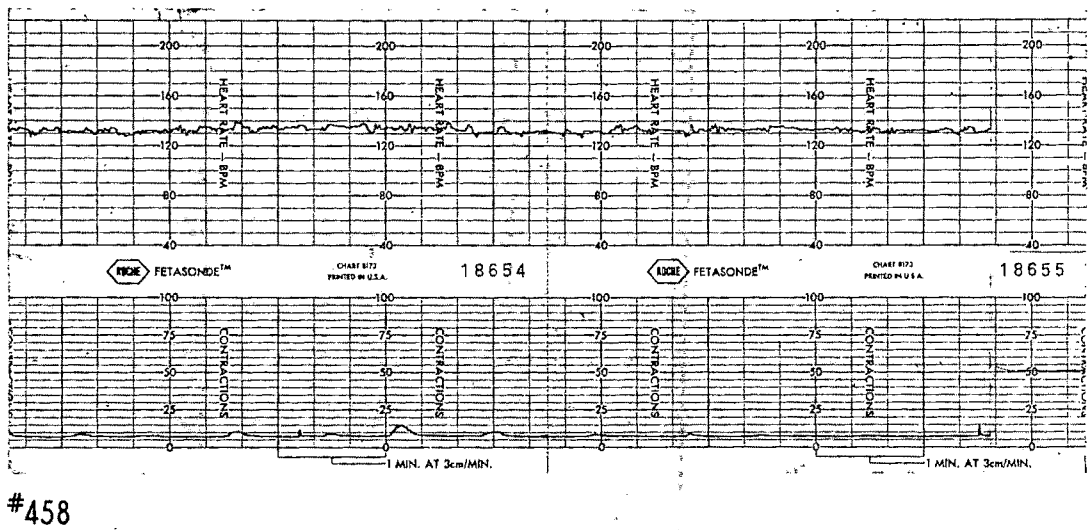


Fig. 5. Base-line record showing decreased base-line variability and no accelerations. An adequate study was not obtained. Fetal death occurred within 48 hours of the record.

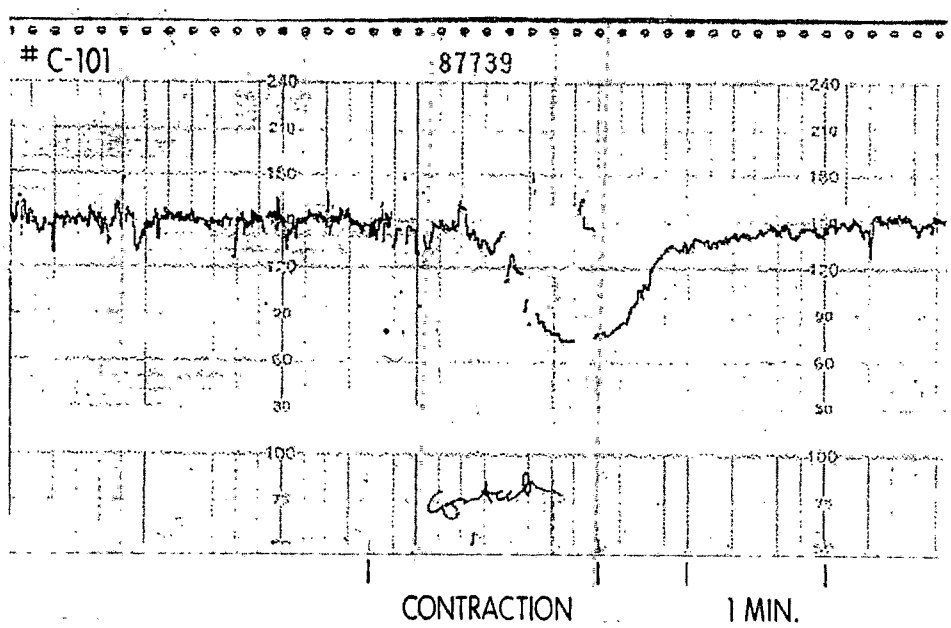


Fig. 6. Antepartum cardiotachometry revealing a positive study with spontaneous uterine activity in a chronically hypertensive patient at 35 weeks. No accelerations were noted. The record was transmitted by telecopier to the Center for consultation, and a neonatal transport team was dispatched to attend the delivery.

greater diabetic (two with hypertension), four were chronically hypertensive (two with superimposed toxemia), and two had documented postmaturity. One patient reporting only decreased fetal movement showed a positive study period and was delivered by cesarean section after a trial of labor and the demonstration of fetal distress.

Accelerations of the fetal heart rate. Table IV shows increased perinatal morbidity associated with the absence of fetal heart rate accelerations. The difference is significant at a p level of 0.05. Both patients with fetal death showed no accelerations of the fetal heart rate during their inadequate studies. In this series, 12 per cent of patients with studies showing accelerations of the fetal heart rate also had late decelerations with adequate uterine activity. Seventeen per cent of pa-

Table V. Fetal heart rate—uterine activity study

Outcome	*Negative study (No. = 163)*		*Positive study (No. = 17)*	
	With accelerations	*Without accelerations*	*With accelerations*	*Without accelerations*
No. of patients	114	49	10	7
Good outcome (Group 1)	104 (91%)	30 (61%)	7 (70%)	0
Over-all increased morbidity (Group 2)	10 (9%)	19 (39%)	3 (30%)	7 (100%)
Intrapartum fetal distress	2	5	2	6
Falling estriol	0	0	1	2
Low Apgar score	5	6	1	3
Neonatal morbidity	6	12	1	4

tients without fetal heart rate accelerations showed similar periodic decelerations.

Accelerations and study morbidity groups. The differentiation of morbidity groups associated with positive study periods and the recognition of the over-all association of the lack of fetal heart rate accelerations with increased perinatal morbidity suggested an examination of each study morbidity group for fetal heart rate accelerations. Table V demonstrates that 100 per cent of patients with studies showing late decelerations and no accelerations of the fetal heart rate were in high-morbidity Group 2. Patients exhibiting a positive study period with accelerations of the fetal heart rate may or may not show increased perinatal morbidity. The importance of a combined evaluation of fetal heart rate accelerations and fetal heart rate response to spontaneous or induced uterine activity is shown in Table V.

It is of interest to note that a positive oxytocin challenge test (study period) can occur with accelerations of the fetal heart rate and may be associated with increased morbidity. A negative study period with accelerations is associated with significantly less morbidity than a negative study period without accelerations or a positive study with accelerations of the fetal heart rate ($p < 0.05$). A positive study period without accelerations is associated with significantly increased morbidity ($p < 0.05$). The statistical method of multiple comparisons with the use of separate tests and Bonferroni's inequality to approximate the levels was used.[9]

Comment

The "oxytocin challenge test" or the "contraction stress test" has been studied extensively over the past several years. In prospective studies, the negative test has been shown to be reassuring regarding fetal well-being.[7, 10, 11] The significance of the positive oxytocin challenge test remains somewhat uncertain. In the report of Ewing and associates[5] the majority of patients with a positive oxytocin challenge test developed fetal distress in labor, necessitating delivery by cesarean section. Christie and Cudmore[11] reported nine positive oxytocin challenge tests with no correlation between a positive test, low estriol levels, or the occurrence of fetal distress in labor. The series reported by Cooper and colleagues[12] revealed a high cesarean section rate for fetal distress in patients with a positive oxytocin challenge test. Freeman[7] has summarized a rather confused picture regarding lack of correlation of oxytocin challenge test results and tolerance of the fetus during labor. He recounts that most patients who have had a positive test will show late decelerations in labor but that a significant number of patients with such tests will show no late decelerations when monitored during labor. In the current study, we have examined the relationship of fetal heart rate changes associated with uterine activity and perinatal outcome. In our series, 50 per cent of the patients with a positive study (similar to an oxytocin challenge test) were at risk for increased perinatal morbidity. The majority of patients with the higher morbidity came from diagnostic categories of Class B or greater diabetes, chronic hypertension, or postmaturity.

We have noted that accelerations in the fetal heart rate may occur with a positive contraction-stimulation test. Schifrin and colleagues[10] noted that when accelerations were present, no fetus developed late decelerations with induced contractions. Freeman[7] has stated that a positive oxytocin challenge test is often but not always associated with a decrease in variability and an absence of fetal heart rate accelerations with movement. We have reported late decelerations with accelerations of the fetal heart rate.

Studies have shown that a fixed heart rate is present with problems of neurocirculatory control such as exhibited by patients in deep coma[13] and premature and dying fetuses and newborn infants.[14] The spinal accelerator center responsible for heart rate acceleration, which is mediated via the thoracolumbar division

of the autonomic nervous system, is under the control of higher centers, probably centrally located in the posterior hypothalamic region.[8] The lack of acceleration of the fetal heart rate, often associated with fetal activity, may be a sign of central nervous system depression. Our data suggest that this indicator of central nervous system depression, associated with the lack of placental respiratory reserve demonstrated by late periodic decelerations of the fetal heart rate, may be predictive of the patient at high risk for perinatal morbidity. Conversely, late deceleration occurring with coexisting accelerations of the fetal heart rate may be an earlier sign of compromise—the central nervous system not yet being depressed.

In the current study, two fetal deaths were noted. Unfortunately, in neither case was an adequate study performed within one week of death. However, the base-line heart rate recording revealed the distinct lack of accelerations of the fetal heart rate. This is consistent with data from Rochard and co-workers[15] and Rüttgers and associates,[16] demonstrating that fetuses with a persistent decrease in base-line variability and an absence of accelerations with movement have a much poorer prognosis.

Conclusions

The results suggest that the absence of accelerations of the fetal heart rate is associated with an increased risk for perinatal morbidity. Late periodic fetal heart rate decelerations may occur in response to uterine activity in the antepartum period when accelerations of the fetal heart are present. Data are not yet sufficient to indicate the significance of late decelerations associated with accelerations of the fetal heart rate. The presence of late periodic fetal heart rate decelerations, in the absence of accelerations of the fetal heart rate, is highly suggestive of increased perinatal morbidity.

REFERENCES

1. Myers, R. E., Mueller-Heubach, E., and Adamsons, K.: Predictability of the state of fetal oxygenation from a quantitative analysis of the components of late deceleration, Am. J. Obstet. Gynecol. **115:** 1083, 1973.
2. Beard, R. W.: The detection of fetal asphyxia in labor, Pediatrics **53:** 157, 1974.
3. Hon, E. H., and Wohlgemuth, R.: The electronic evaluation of fetal heart rate. IV. The effect of maternal exercise, Am. J. Obstet. Gynecol. **81:** 361, 1961.
4. Ray, M., Freeman, R., Pine, S., et al.: Clinical experience with the oxytocin challenge test, Am. J. Obstet. Gynecol. **114:** 1, 1972.
5. Ewing, D. E., Farina, J. R., and Otterson, W. N.: Clinical application of the oxytocin challenge test, Obstet. Gynecol. **43:** 563, 1974.
6. Freeman, R. K.: The clinical value of antepartum fetal heart rate monitoring, *in* Gluck, L., editor: Modern Perinatal Medicine, Chicago, 1974, Year Book Medical Publishers, Inc., pp. 163-177.
7. Freeman, R. K.: The use of the oxytocin challenge test for antepartum clinical evaluation of uteroplacental respiratory function, Am. J. Obstet. Gynecol. **121:** 481, 1975.
8. Lee, C. Y., DiLoreto, P. C., and O'Lane, J. M.: A study of fetal heart rate acceleration patterns, Obstet. Gynecol. **45:** 142, 1975.
9. Miller, R. G.: Simultaneous Statistical Inference, New York, 1966, McGraw-Hill Book Company, Inc., pp. 67-70.
10. Schifrin, B. S., Lapidus, M., Doctor, G. S., et al.: Contraction stress test for antepartum fetal evaluation, Obstet. Gynecol. **45:** 433, 1975.
11. Christie, G. B., and Cudmore, D. W.: The oxytocin challenge test, Am. J. Obstet. Gynecol. **118:** 327, 1974.
12. Cooper, J. M., Soffronoff, E. C., and Bolognese, R. J.: Oxytocin challenge test in monitoring high-risk pregnancies, Obstet. Gynecol. **45:** 27, 1975.
13. Vallbona, C., Cardus, D., Spencer, W. A., et al.: Patterns of sinus arrhythmia in patients with lesions of the central nervous system, Am. J. Cardiol. **16:** 379, 1965.
14. Hon, E. H., and Lee, S. T.: Electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death, further observations, Am. J. Obstet. Gynecol. **87:** 814, 1963.
15. Rochard, F., Schifrin, B. S., Sureau, C., et al.: Nonstressed fetal cardiotachometry in the antepartum period, Am. J. Obstet. Gynecol. In press.
16. Rüttgers, H., Xubli, F., Haller, U., et al.: Die antepartale fetale Herzfrequenz. I. Verhalten von Grundfrequenz, Fluktuation und Dezelerationen in der ungestörten Schwangerschaft, Z. Geburtshiefe Perinatol. **176:** 294, 1972.

Classification of human fetal movement

ILAN TIMOR-TRITSCH, M.D.
IVAN ZADOR, M.Sc.
ROGER H. HERTZ, M.D.
MORTIMER G. ROSEN, M.D.
Cleveland, Ohio

A study of fetal activity was undertaken as the first step in a series of physiologic fetal movement studies. A simple, safe, noninvasive, clinically applicable method for studying fetal movement with a tocodynamometer is described. Four basic types of fetal movement have been seen and defined in terms of their durations, recorded patterns, and descriptive terminologies for identifying each movement.

QUICKENING IS THE first maternal perception of fetal activity and often is a useful index of gestational age. It is through this fetal movement (FM) that a mother first becomes acquainted with her fetus, and with time the activity becomes reassuring to both mother and physician. Clinical experience suggests that fetal activity and fetal health may be related.

In order to understand more clearly the clinical significance of fetal movement, a study program was undertaken to record and to describe the kinds of activity observable with a tocodynamometer. In this report we will describe FM in terms of its frequencies, amplitudes, and durations and their subjective discriminators. Since this is a descriptive study identifying types of activity which may be present, no attempt will be made to ascribe significance to these movements in terms of fetal well-being.

Selected historical background

Reinold[1] studied FM as early as the tenth week of pregnancy with the aid of ultrasound. He described two kinds of movements: a strong sudden movement and a slow movement. Reinolds observed in retrospect that when the fetal movements were absent the fetus was at risk.

Sterman,[2] in 1967, described "kicks," "squirming," "general agitation," and "fetal hiccups," but his interest was directed mainly at describing the correlation between maternal sleep and fetal motor activity. Sadovsky and colleagues[3] attempted to correlate daily fetal movement count with pregnancy outcome but did not attempt to distinguish between different kinds of movements or activity patterns. Hems[4] associated "jerking fetal activity" with fetal distress and cord involvement during labor and delivery.

In 1905, Ahlfeld[5] recorded human fetal respiratory movements. Later, respiration in utero was studied extensively in experimental animals by Snyder and Rosenfeld[6, 7] and Bonar and colleagues.[8]

Using the guinea pig as an experimental model, Rosen[9] associated gasping respiratory movements with fetal distress and with flattened fetal electroencephalographic patterns. Davis and Potter[10] in a radiologic study documented "amniotic fluid breathing" in the absence of distress in human fetuses. Howatt and co-workers[11] were able to measure the fluid displacement during breathing movements in fetal lambs.

Boddy and associates[12, 14, 15] and Dawes and colleagues[13] introduced ultrasound monitoring of fetal respiratory movements into antepartum clinical management of high-risk pregnancies. More recently, fetal heart rate (FHR) accelerations have been associated with FM.[16]

Method

Thirty women with gestational ages ranging between 26 weeks and term, who were admitted to the hospital

From the Department of Obstetrics and Gynecology, Cleveland Metropolitan General Hospital/Case Western Reserve University, School of Medicine.

Supported in part by Grants 5M01-RR00210-12 and HD 05566-01A1 from the National Institutes of Health, United States Public Health Service, and by The Grant Foundation, Inc.

Received for publication December 1, 1975.

Revised March 2, 1976.

Accepted March 18, 1976.

Reprint requests: Dr. Ilan Timor-Tritsch, Cleveland Metropolitan General Hospital, Department of Obstetrics and Gynecology, 3395 Scranton Rd., Cleveland, Ohio 44109.

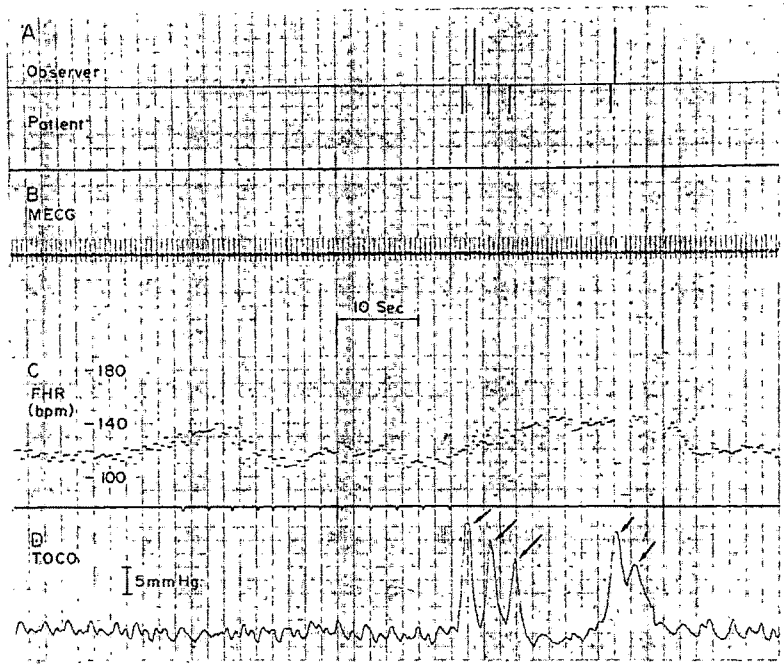


Fig. 1. The four-channel strip-chart record. *A,* Observer's (upward) and patient's (downward) marks. *B,* Maternal electrocardiogram (usually Lead II). *C,* Printout of instantaneous FHR recorded by the ultrasound array transducer. *D,* Printout of the tocodynamometer placed over the uterus. Two rolling movements (arrows) are shown on this tracing. The durations of the two movements are 8 and 3 seconds, respectively. Note the acceleration pattern of the FHR with a temporary loss of signal during the second movement.

for the management of obstetric complications, were studied. Thus, as noted in the introduction, the data in no way represent normal population characteristics.

The total monitoring time for all patients was 58 hours and 30 minutes. An average of almost two hours (117 minutes) was spent monitoring each patient. No patients were in labor, and the amniotic membranes were intact in all. During the monitoring period, patients were lying comfortably in a semi-Fowler position. Monitoring in the lateral recumbent position was not done in this study. Maternal movements were voluntarily restricted. Extraneous noise was minimized.

An ultrasound amplifier* coupled with a cardiotocograph† was used for recording the instantaneous fetal heart rate which was written out on a four-channel physiologic recorder‡ (Fig. 1). One channel of the recorder was modified to note fetal movements felt by the mother and by the physician. The patient and the observer operated a separate switch every time a fetal movement was detected. Upward deflection of the recording pen indicated movement felt by the physician while downward deflection indicated maternal observations. The presence of an observer is required to note movement "artifacts" such as maternal movement, coughing, sneezing, deep breathing, laughing, cigarette smoking, etc.

Maternal abdominal wall movements were recorded with an abdominal pressure transducer* connected to a pressure amplifier.† The pressure transducer was placed on the mother's abdomen over a well defined prominent part of the fetal body, but not necessarily over the same part each time. Fetal position and the placental location was determined by ultrasound employing a B-mode scanner.‡ The maternal electrocardiogram was recorded on the remaining channel of the chart recorder.

Results

A total of 1,278 individual movements were recorded. The data were analyzed visually. Different basic types of movements were described on the basis of the duration, shape, and amplitude and the observer's

*HP-15180, Hewlett-Packard Co., 1501 Page Mill Rd., Palo Alto, California 94304.

†HP-8020A, Hewlett-Packard Co.

‡HP-7754A, Hewlett-Packard Co.

*B2264, Corometrics Medical Systems, Inc., 2 Barnes Industrial Park Rd., Wallingford, Connecticut 06492.

†8800, Hewlett-Packard Co.

‡Echoview IX. Picker Scientific Apparatus Div., Picker Corp., 1020 London Rd., Cleveland, Ohio 44110.

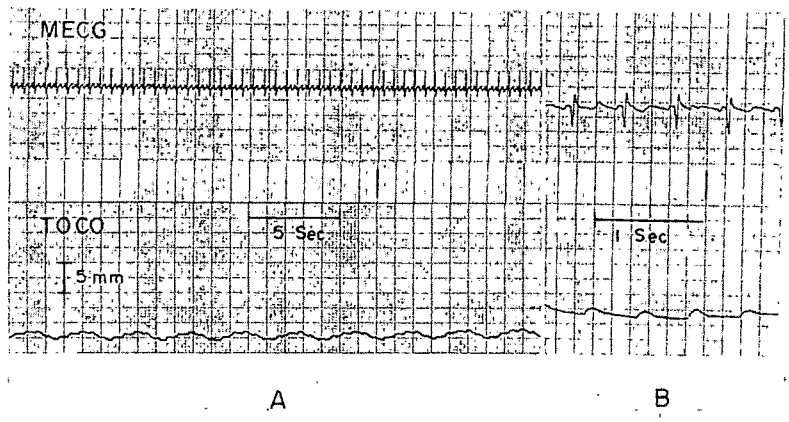


Fig. 2. The two most common artifacts recorded by the tocodynomometer. *A*, Maternal respiratory wave with superimposed abdominal aortic pulsations. *B*, Maternal aortic pulse which coincides with the T wave of the simultaneously recorded maternal electrocardiogram.

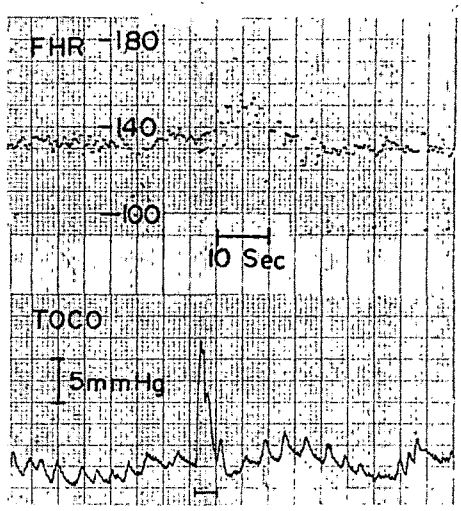


Fig. 3. Simple movement. The duration of the movement is 4 seconds (⟷). Note the indented falling edge of the wave and the acceleration in the FHR during the movement.

palpation and visual perception of the specific FM, as well as some of the maternal anecdotal descriptions. Simultaneous M-mode recording was used in certain movements to provide additional information as to the identity of the movement. In addition, two basic maternal movement artifacts were noted and described below.

The maternal respiratory pattern (Fig. 2, *A*) ranges in amplitude between 2 and 10 mm. Hg with a rate of 14 to 22 respirations per minute. The maternal aortic pulse is displayed as a smaller wave, sometimes superimposed on the maternal respiration wave. Its peak coincides with the T wave of the recorded maternal electrocardiogram as seen in Fig. 2, *B*.

- **Fetal movement types.** Four basic types of movements were described.

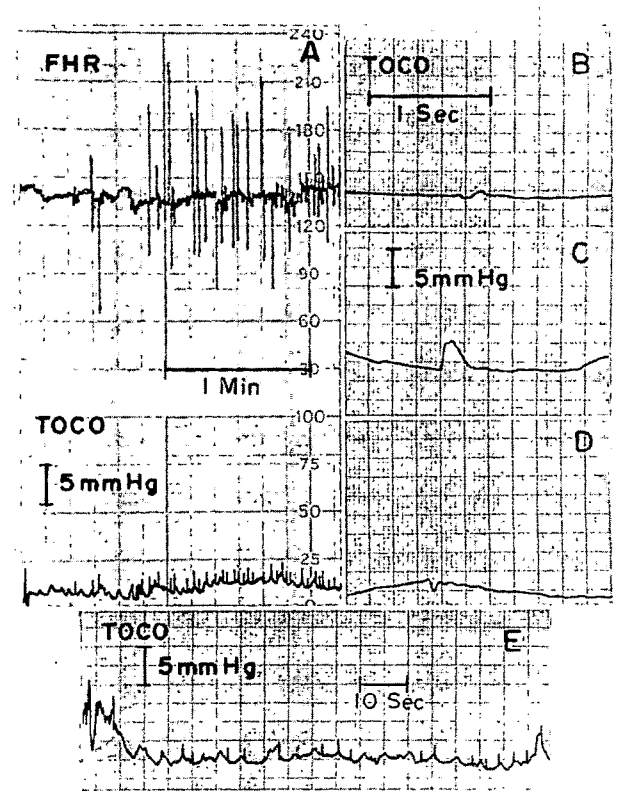
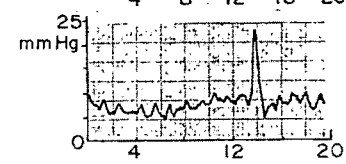
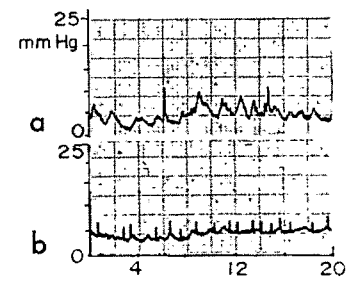
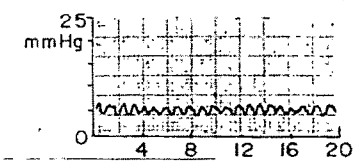


Fig. 4. High-frequency movement. *A*, Typical small spikes of the repetitive high-frequency movement recorded during clinical monitoring with a paper speed of 3 cm. per minute. Note the FHR artifacts when the signal is disturbed by this movement. *B* to *D*, Isolated high-frequency movement with biphasic, positive, and negative wave forms, respectively, recorded at a paper speed of 25 mm. per second.

Rolling movement (Fig. 1, *D*). Three hundred and fifty-eight movements of this type were recognized.

DESCRIPTION. This is a sustained and rolling movement which seemed to be associated with the entire

Table I. Cummulative table of all FM types. The wave forms are shown at the same scale factors

Types of fetal motor activity	*Duration*	*Amplitude*	*Remarks*	*Typical wave form*
1. Rolling movement	Mean 14.0 sec. S.D. ± 7.9 sec.	Undefinable but usually the highest of all	Well perceived by observer or mother	
2. Simple movement	Mean 3.0 sec. S.D. ± 1.7 sec.	Undefinable	Usually well perceived by observer or mother	
3. *High-frequency movement*	0.12-0.4 sec.	Approximately 2-10 mm. Hg (may be a positive, negative, or biphasic deflection)	Well perceived by observer or mother	
a. Isolated				
b. Repetitive				
4. Respiratory movement	0.4-1.2 sec.	2-5 mm. Hg	May be superimposed on maternal respiratory wave. Perceived by mother or observer	

fetal body in motion. A large transducer displacement was seen. The movement was readily palpated by both mother and observer.

DURATION. The calculated mean duration was 14.0 seconds with a standard deviation of 7.9 seconds. The range was between 4 and 36 seconds.

WAVE SHAPE. It was usually biphasic or multiphasic. The spikes were of different amplitudes. Some of the swings during the rolling movement dropped below the base line, and others resulted in an elevation of the uterine pressure base line. The return to the base line was slurred and gradual.

AMPLITUDE. It is difficult to define and compare accurately the amplitude of this fetal movement. This problem will be discussed later.

FETAL HEART RATE. Several comments may be made: At times, the signal was lost because the fetal heart moved out of the ultrasound beam (Fig. 1, *C*). If the FHR remained readable during the movement, acceleration was noted and usually lasted through the duration of the movement. Additional "spikes" in the recorded movement pattern sometimes coincided with an additional small "hump" in the original acceleration pattern.

Simple movement (Fig. 3). Three hundred and fifty-eight simple movements were analyzed.

DESCRIPTION. The movement was relatively short and easily palpable; it felt as though it originated from a fetal extremity. It was usually associated with a visible displacement of the abdominal wall. It was perceived by both mother and observer.

DURATION. The calculated mean duration was 3.0 seconds with a standard deviation of 1.7 seconds. The range was from 1 to 15 seconds.

WAVE SHAPE. There was usually one single spike. Sometimes the wave was altered slightly or indented on the rising or falling limb by a superimposed maternal respiratory wave. There usually was no elevation in the uterine base-line pressure.

AMPLITUDE. The amplitude could not be quantified with this technique.

FETAL HEART RATE. The FHR acceleration pattern was usually shorter and followed the shorter time span of this type of movement. The acceleration seemed to be uniform in shape and returned to the base line without fluctuation.

High-frequency movement (Fig. 4).

DESCRIPTION. These were short, easily palpable, and

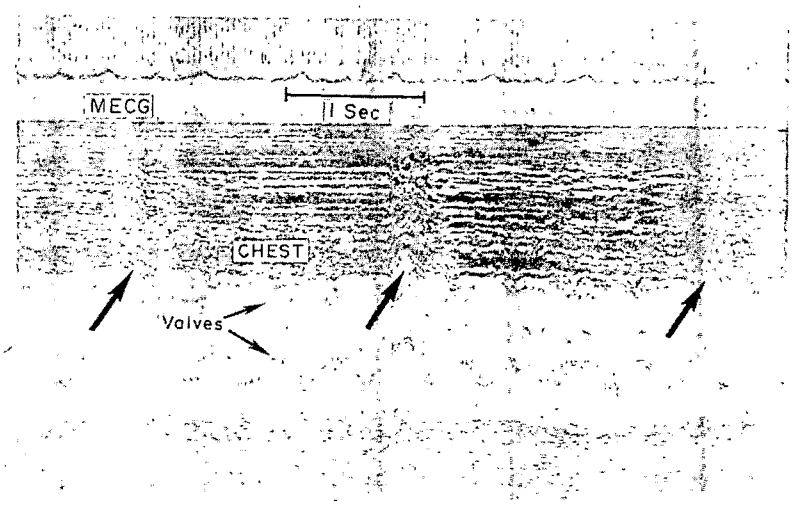


Fig. 5. Ultrasound M-mode recording during repetitive high-frequency movement. Arrows indicate displacement of fetal chest wall.

sometimes readily seen movements of the fetus. The mother described the movements as short, kicking, felt throughout the entire abdomen, and not easily localized.

DURATION. The observed range was 0.12 to 0.4 second. Since the range was so limited, means were not calculated.

AMPLITUDE. The amplitude of this movement was relatively low and ranged between 2 and 10 mm. Hg. It seldomly exceeded the magnitude of the maternal respiratory wave but could be readily distinguished from this because of its higher frequency and steady amplitude throughout the entire tracing.

WAVE SHAPE. This was usually a polar deflection but was sometimes biphasic, depending on the location of the transducer (Fig. 4, *B, C,* and *D*). This wave form was perhaps the only fetal movement which could not easily be confused with artifacts of maternal origin. It is also distinct from the other forms of FM's.

In the high-frequency–movement patterns defined here, we were able to define two expressions, both with the same subjective feeling by the mother or the clinician and both with the same amplitude and duration as seen on the strip chart. They differed only in that at times they appeared as *isolated* wave forms and at other times in *repetitive* sequences.

1. The *isolated high-frequency movement* occurred in single episodes, not in any way time linked. It was mixed with the simple and the rolling movements and was present in all studied patients. Five hundred and sixty-two movements of this kind were counted.

2. The *repetitive high-frequency movement* (Fig. 4, *A* and *E*) occurred in cycles which lasted between five and 18 minutes with an observed rate of 15 to 25 movements per minute. It was noted in 10 patients. Usually, no other type of FM was present during the same period of time. This kind of movement was not included in the histogram (Table I).

In seven cases where the repetitive high-frequency movement was observed and recorded, we attempted to localize its origin. By questioning the patient and by continuous external palpation, we felt certain that the underlying movement did not come from the fetal limb or head. The recorded wave-form pattern (duration and amplitude) was clearly different from any other fetal movement observed in the study. We speculated that the underlying cause might be a sudden movement of the fetal chest wall as might occur in hiccuping or gasping.

To confirm this assumption, the fetal chest and heart were visualized with an ultrasound B-scan. The distance between the maternal abdominal wall and the fetal chest wall was measured. After the fetal heart was localized, the ultrasound scan was switched to M-mode. The movements of the fetal chest wall and fetal heart were then recorded. Although this high-frequency movement occurred at unpredictable times, successful recording of this repetitive movement with the ultrasound system was obtained in two cases (Fig. 5). In those two cases, the high-frequency movement was also identified by both palpation and the patient's perception. It is suggested that this movement is produced by rapid fetal chest wall movement.

Respiratory movement (Fig. 6).

DESCRIPTION. The underlying cause was a respiration-like movement of the fetal chest wall. It could be felt by the mother or observer. Sometimes it was seen by the observer.

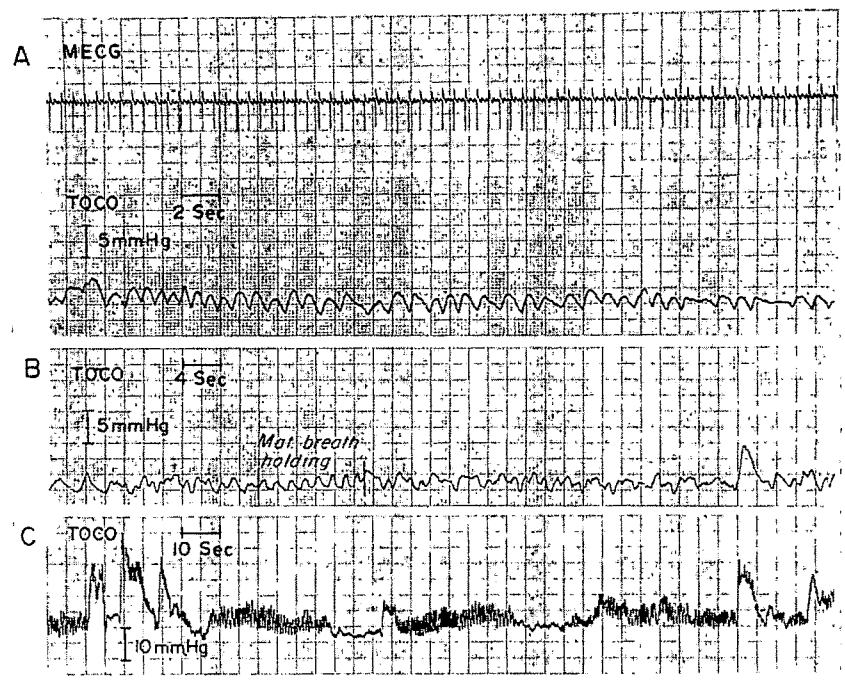


Fig. 6. Fetal respiratory movement recorded by the tocodynamometer. *A*, Simultaneously recorded maternal electrocardiogram and fetal respiration. *B*, Fetal respiration superimposed on maternal respiration. Maternal breath-holding reveals the "pure" fetal pattern. *C*, The irregular appearance of fetal respiratory movement.

DURATION. The range of the isolated wave was 0.4 to 1.2 seconds. Once again, the range was so limited that the means were not calculated.

AMPLITUDE. This could be calculated and was usually 2 to 5 mm. Hg.

WAVE FORM. The isolated wave shape resembled a positive section sinewave. Usually it was repetitive, and the frequency varied between 30 and 90 per minute. (Fig. 6, *A*). At times it was superimposed on the maternal respiratory wave, but, during voluntary maternal breath-holding, the "pure" wave form became obvious (Fig. 6, *B*). It could be easily differentiated from the maternal aortic pulse wave by means of simultaneous recording of the maternal electrocardiogram (Fig. 6, *A*).

In order to document the origin of this movement, we studied the same seven patients who had the M-mode ultrasound studies described earlier. The simultaneous recording of the fetal chest wall displacement by ultrasound and the resulting displacement of the maternal abdominal wall by the tocotransducer yielded the same recorded wave forms and frequencies (Fig. 7). We were able to show breathing movements by ultrasound in all seven patients. With the tocotransducer alone, we recorded respiratory patterns in nine patients. These patterns were irregular (Fig. 6, *C*). At times they lasted unchanged for several minutes, and at other times they ceased, only to reappear in seconds or minutes.

The four main movement types are presented in Table I. This table made it possible to compare the FM types with the use of the same scale factors.

Comment

As noted earlier, this study was to identify and describe fetal motor activity as a first step in learning more about the physiology and pathophysiology of FM in utero. The study was also undertaken to determine which monitoring instruments were appropriate. We looked for a simple monitoring system with the hope that our results would have potential clinical applicability.

FM has been studied with the use of electromagnetic, tocodynometric, and, recently, ultrasound techniques. With real-time ultrasound, movement can be accurately visualized. But, in order to study fetal motor activity patterns, several hours of continuous observation are required; thus, ultrasound equipment in its present stage of development is impractical for this study. Monitoring FM with a tocotransducer is simple, safe, inexpensive, noninvasive, and potentially clinically applicable. Therefore, FM may be studied by clinicians using standard monitoring equipment. In our study, ultrasound was used only to document the

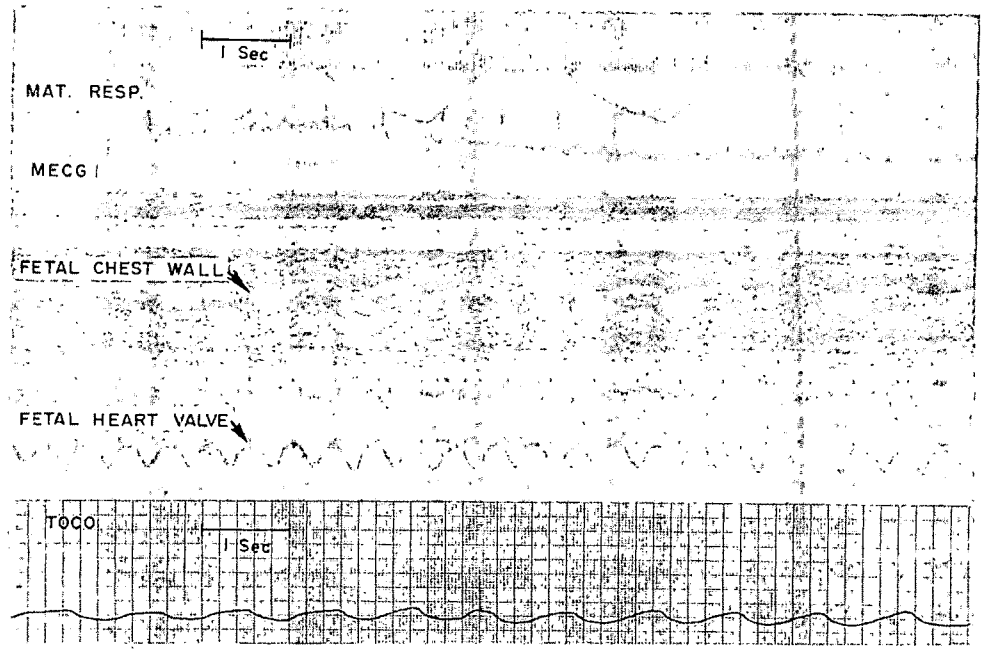


Fig. 7. Simultaneous ultrasound M-mode and tocodynamometer recording of fetal respiration. Note the almost identical wave forms of the fetal chest wall and the abdominal *(TOCO)* recording of the same movement.

origin of specific movements and to record the FHR.

From our experience, it is clear that FM can best be categorized on the basis of the *duration* and the *pattern* of the recorded movement. While the amplitude of the wave pattern may be examined, it is not a defining characteristic of the movement. Amplitude is affected by transducer location (relative to specific areas of the uterus and the fetus), the distance between the transducer and the fetus, and fetal size. Other factors, including obesity, an anteriorly located placenta, and hydramnios may influence the amplitude. These same factors do not change the duration or the basic pattern of the FM. Thus, with a tocotransducer, it is impossible to determine more than the relative amplitude or force of the movement.

The *duration* of the movement may be the most important variable. On the basis of duration, high-frequency movement (0.1 to 0.4 second) and respiratory movement (0.4 to 1.2 seconds) can be differentiated from the mean duration of the simple and rolling movements of 3.0 and 14.0 seconds, respectively. In rare instances, one may observe prolonged motor activity (>36 seconds). This activity is characterized by a series of individual movements (variable sequence) sometimes lasting as long as two to three minutes. We cannot offer any explanation for this relatively infrequent observation at this time.

The *recorded* pattern of the movement is also an important variable. Different types of movements are clearly distinguishable on the basis of their recorded pattern (Table I).

The best transducer location is found by trial and error. Rolling and simple movements are easily recorded and recognized. High-frequency movements and respiratory movements are best recorded with the transducer placed over the fetal trunk.

Three types of fetal movement were present in *all* monitoring tracings: the rolling, simple, and isolated high-frequency–movement types. A total of 1,278 of these isolated movements were counted. Their relative occurrence was 28, 28, and 44 per cent, respectively. The histogram (Fig. 8) was based on one simple parameter. The duration of the movement shows the existence of three statistically different ($p < 0.001$) groups.

Rolling movement was present in all cases. It was detected and recorded as early as 26 weeks of pregnancy. The multiphasic, sometimes negative, deflection arbitrarily defined as (lowering of pressure beneath the transducer) patterns of this movement type results from the extensive rolling of fetal parts which move the transducer tip back and forth, causing its displacement.

Simple movement was also present in all cases. It was also recorded as early as 26 weeks of pregnancy. This movement must be differentiated from artifacts such as coughing, deep breathing, and movements of the

patient because of their similar configuration. The identification signal given by the patient is of importance in these situations.

We believe that the origin of high-frequency movement is a sudden chest wall movement. Two subjective descriptors of such types of activity are gasping and hiccuping.

Fetal respiratory movements (fetal "breathing") often may be detected but must be carefully differentiated from the maternal aortic pulse which at times is similar in frequency, duration, pattern, and amplitude. This is accomplished by simultaneous recording of the maternal electrocardiogram. According to Boddy and Robinson[14] and Boddy and Dawes,[15] fetal breathing is usually irregular. Our data support their observations. The two movements originating from the fetal chest wall were observed starting at 26 to 27 weeks of gestation.

As we stated earlier, we cannot yet make suggestions as to the differences which may be present in a normal and abnormal pregnancy population, and we cannot make statements regarding maturation, effect of drugs, or smoking. All these have to be part of other studies.

It is apparent from this study that various kinds of

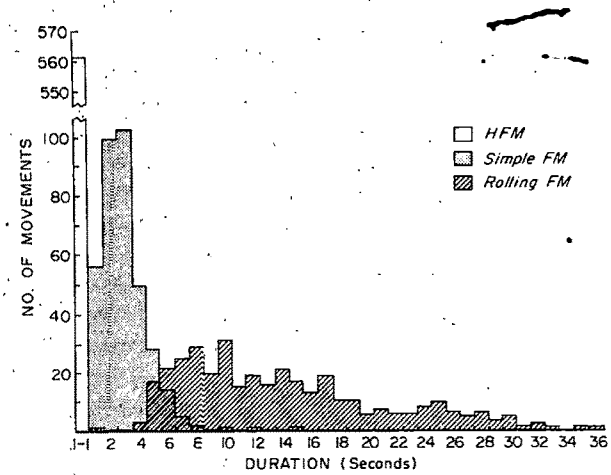


Fig. 8. The histogram of 1,278 movements according to their durations. Included are the rolling, simple, and repetitive high-frequency movement *(HFM)* types.

FM exist prior to birth as they do in the neonate or adult after birth. The origin of the stimuli for these observed behaviors, their controlling systems, and their relationships to fetal neurological development and fetal well-being remain to be understood.

REFERENCES

1. Reinold, E.: Clinical value of fetal spontaneous movements in early pregnancy, J. Perinatol. Med. **1:** 65, 1973.
2. Sterman, M. B.: Relationship of intrauterine fetal activity to maternal sleep stage, Exp. Neurol. **19:** 98, 1967.
3. Sadovsky, E., Yaffe, H., and Polishuk, W. Z.: Fetal movement monitoring in normal and pathologic pregnancy, Int. J. Gynecol. Obstet. **12:** 75, 1974.
4. Hems, D. A.: Palpable regular jerking movements of the human fetus. A possible respiratory sign of fetal distress, Biol. Neonate **23:** 223, 1973.
5. Ahlfeld, F.: Die intrauterine Tatigkeit der Thorax- und Zwerch-fellmuskulatur. Intrauterine Atmung, Monatsschr. Geburtshilfe Gynaekol. **21:** 143, 1905.
6. Snyder, F. F., and Rosenfeld, M.: Direct observation of intrauterine respiratory movements of the fetus and the role of carbon dioxide and oxygen in their regulation, Am. J. Physiol. **119:** 153, 1937.
7. Snyder, F. F., and Rosenfeld, M.: Intrauterine respiratory movements of the human fetus, J. A. M. A. **108:** 1946, 1937.
8. Bonar, B. E., Blumenfeld, C. M., and Fenning, C.: Studies of fetal respiratory movements, Am. J. Dis. Child. **55:** 1, 1938.
9. Rosen, M. G.: Effects of asphyxia on the fetal brain, Obstet. Gynecol. **29:** 687, 1967.
10. Davis, M. E., Potter, E. L.: Intrauterine respiration of the human fetus, J. A. M. A. **131:** 1194, 1946.
11. Howatt, W. F., Humphreys, P. W., Normand, D. C. S., and Strang, I. B.: Ventilation of liquid by the fetal lamb during asphyxia, J. Appl. Physiol. **20:** 496, 1965.
12. Boddy, K., and Mantell, C. D.: Observations of fetal breathing movements transmitted through maternal abdominal wall, Lancet **2:** 1219, 1972.
13. Dawes, G. S., Fox, H. E., Leduc, B. M., Liggins, G. C., and Richards, R. T.: Respiratory movements and rapid eye movement sleep in the foetal lamb, J. Physiol. **220:** 119, 1972.
14. Boddy, K., and Robinson, J. S.: External method for detection of fetal breathing in utero, Lancet **2:** 1231, 1971.
15. Boddy, K., and Dawes, G. S.: Fetal breathing, Br. Med. Bull. **31:** 3, 1975.
16. Lee, C. Y., DiLoreto, P. C., and O'Lane, J. M.: A study of fetal heart rate acceleration patterns, Obstet. Gynecol. **45:** 142, 1975.

Respiratory distress syndrome with mature lecithin/sphingomyelin ratios: Diabetes mellitus and low Apgar scores

A. C. CRUZ, M.D.
W. C. BUHI, M.S.
S. A. BIRK, R.N.
W. N. SPELLACY, M.D.
Gainesville, Florida

A detailed study was made of 150 women delivered of their infants within 72 hours of an amniocentesis where the lecithin/sphingomyelin (L/S) ratio was 2.0 or greater. There were nine neonates with respiratory distress (6.0 per cent). There were two neonatal deaths, both due to severe congenital heart disease. A mature amniotic fluid L/S ratio predicts a newborn infant who will not have respiratory distress syndrome (RDS) in most pregnancies. There is a significantly increased risk of RDS in neonates with a mature L/S ratio if the mother has insulin-dependent diabetes or if there is a resulting low Apgar score. The method of delivery (cesarean section or vaginal) does not affect the frequency of RDS where the L/S ratio is 2.0 or more.

PULMONARY IMMATURITY and its sequelae have been a major concern of clinicians when early delivery was deemed necessary for medical reasons. Although fetal death in utero can be prevented by such terminations, neonatal respiratory problems and eventual death may occur, and this would not alter the over-all perinatal mortality rate. With the introduction by Gluck and associates[11] of a method for estimating fetal lung surfactant activity, perinatologists now can feel more confident of the infant outcome when early termination of pregnancy is indicated. There are many ways of evaluating fetal surfactant activity.[11, 24, 25] The amniotic fluid lecithin/sphingomyelin (L/S) ratio has been the most widely used. An L/S ratio is considered mature at 2.0 or more, and this usually indicates that the newborn will not have respiratory distress due to lung immaturity.

The purpose of the present study was to evaluate the role of maternal complications, neonatal Apgar scores and the method of delivery in contributing to the risk of respiratory distress syndrome (RDS) when a mature amniotic fluid L/S ratio existed.

From the Department of Obstetrics and Gynecology of the University of Florida College of Medicine.

Received for publication September 3, 1975.
Revised February 16, 1976.
Accepted March 1, 1976.

Reprint requests: Dr. Amelia C. Cruz, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida 32610.

Methods

There were 150 women who participated in the study. All of the women had an amniocentesis performed transabdominally after an informed consent was obtained. There were no complications from the procedure. Any fluid which contained blood or meconium was excluded from the study.[5] The L/S ratio was determined by a thin-layer chromatographic technique as previously described.[28] Only those patients delivered of their infants within 72 hours after the amniocentesis where a mature L/S ratio of 2.0 or more was found were included in this study. Following hospital discharge, the maternal and neonatal records were carefully reviewed, and all of the clinical data as well as the laboratory information were put on punch cards. All of the diagnoses of infant RDS were made by neonatologists. Diagnosis of RDS was made when there was clinical evidence of tachypnea, retraction, and grunting, with or without x-ray confirmation, that persisted for more than 24 hours.

The data were divided and analyzed according to the following categories: hypertensive toxemia (63), Rh

Table I. The incidence of neonatal respiratory distress with an aminotic fluid L/S ratio of 2.0+ where a maternal complication existed (No. = 150)

Maternal complication	*Total No.*	*Average gestational age (weeks)*	*No. with RDS**	*%*	*Probability*
None	38	39.6	0	0	—
Hypertension: diastolic 90-109 mm. Hg	37	38.6	2	5.4	N.S.†
Hypertension: diastolic > 110 mm. Hg	26	38.4	2	7.7	N.S.
Rh sensitization	13	37	0	0	N.S.
Class A diabetes	6	40.3	0	0	N.S.
Insulin-dependent diabetes	14	36.4	4	28.5	<0.004
Ruptured membranes (>12 hours)	16	38.6	1	6.3	N.S.

*Refer to Table II for details.

†N.S. Indicates not significantly different from normal.

sensitization (13), diabetes mellitus Class A (6) or Classes B to D (14), premature rupture of the membranes for more than 12 hours' duration (16), and normal pregnancies (38). They were also studied according to the type of delivery which was performed. These included vaginal delivery (80), elective cesarean section (51), or cesarean section after labor (19). The one- and five-minute Apgar scores were determined by anesthesiologists and/or pediatricians with an electrical timer, and these scores were used for grouping to evaluate the effects of early neonatal distress on the occurrence of RDS.

Since these were nonparametric data, they were statistically evaluated with Chi-square analysis, and Fisher's exact test, and the Mann-Whitney U test. Multiple analyses were done in order to evaluate the cross-over effects of several variables. The probability values were taken from two-tailed tables, and only values of less than 0.05 were considered significant.

Results

Table I shows the distribution of cases based on the maternal complication of the 150 patients with a mature L/S ratio; nine infants (6.0 per cent) developed clinical evidence of RDS. There were no neonatal deaths due to hyaline membrane disease. The information on these nine infants with RDS is shown in Table II. There was no evidence of clinical RDS in the groups of women with normal and Rh-sensitized pregnancies and those with gestational diabetes. The frequency of clinical RDS in other groups varied from 5.4 to 28.5 per cent. The frequencies in each subgroup were compared with those for the women with uncomplicated normal pregnancies, and the risk of RDS was significantly elevated in the insulin-dependent diabetic group ($p < 0.004$).

The gestational age in each group ranged from 32 to 42 weeks (average 39.6) for the normal group, 33 to 44 weeks (average 37) for the Rh-sensitized group, 38 to 43 weeks (average 40.3) for those with Class A diabetes, 34 to 39 weeks (average 36.4) for those with Classes B to D diabetes, and 36 to 44 weeks (average 38.6) for those with premature rupture of the membranes (PROM) (>12 hours). The age distributions of the normal and RDS babies were compared with the Mann-Whitney U test which indicates that the two distributions do not differ significantly ($p > 0.40$). There is no reason based on the present data to assume that presence of RDS may be due to a difference in gestational age.

The patients were also grouped according to the method of delivery (Table III). There was no significant increase in the frequency of RDS when either cesarean section group was compared to the vaginally delivered group. There were 80 vaginal deliveries with RDS in seven babies or 8.75 per cent. There were 70 cesarean sections, 51 elective and 19 after labor. There were two babies with RDS in the elective cesarean section group and none in the group with cesarean section after labor. The method of delivery had no influence on the risk for RDS ($p = 0.228$).

The incidence of RDS in normal infants and those with low Apgar scores is shown in Table IV. An analysis of these data shows that RDS is significantly increased in infants with low one-minute Apgar score ($p < 0.006$) and in infants with low five-minute Apgar score ($p < 0.0001$).

These data were further analyzed to determine whether the low Apgar score and insulin-dependent diabetes were separate variables increasing the risk for RDS. Newborn infants with low Apgar scores had the same increased risk of developing RDS whether or not they had insulin-dependent diabetic mothers, and infants of mothers with insulin-dependent diabetes did not have a significantly higher incidence of low Apgar scores when compared to infants of normal pregnancies. Thus, with the use of Fisher's exact-test method of randomization, it was

Table II. Summary of cases of neonatal respiratory distress after amniotic fluid L/S ratio > 2.0

Patient	*Complications*	*L/S*	*Labor*	*Delivery*	*Sex*	*Week's gestation*	*Infant's weight (grams)*	*Apgar score*	
								1 min.	*5 min.*
K. F.	Diastolic blood pressure >90 mm. Hg	2.4	Induced	Forceps	M	44	3,175	1	5
E. G.	Diastolic blood pressure >90 mm. Hg	2.7	None	Elective cesarean section	M	43	3,500	2	3
E. A.	Diastolic blood pressure >110 mm. Hg	2.6	Spontaneous	SVD*	M	39	2,353	5	9
K. S.	Diastolic blood pressure >110 mm. Hg	3.6	Spontaneous	Forceps	M	38	3,345	9	10
R. M.	Class B diabetes	2.5	Induced	SVD	F	36	4,919	6	9
E. W.	Class B diabetes, toxemia	2.4	Spontaneous	SVD	M	34	2,950	4	5
E. G.	Class C diabetes	2.1	None	Elective cesarean section	F	39	2,466	6	8
S. S.	Class B diabetes	8.0	Induced	SVD	M	36	4,100	8	10
C. G.	PROM > 12 hours	2.3	Spontaneous	SVD	M	38	3,317	8	9

*Spontaneous vaginal delivery.

Table III. The incidence of neonatal respiratory distress with amniotic fluid L/S ratio of 2.0+ by method of delivery

Method of delivery	*Total No.*	*Babies with RDS*	*%*
Vaginal	80	7	8.5*
Elective cesarean section	51	2	2.9*
Cesarean section after labor	19	0	

*Probability not significant.

Table IV. The incidence of neonatal respiratory distress with an amniotic fluid L/S ratio 2.0+ according to the Apgar scores

Apgar score	*Total No.*	*No. with RDS*	*%*
One-minute Apgar scores			
7 or greater	115	3	2.6
≤6	35	6	17.1*
Five-minute Apgar scores			
7 or greater	139	6	4.3
≤6	11	3	27.3†

*$p < 0.006$.
†$p < 0.0001$.

shown that these two variables were independent of each other.

Comment

Maternal, fetal, and placental disease have been shown to either accelerate or delay the gestational time of appearance of a mature amniotic fluid L/S ratio.[12] Generally, once a mature L/S ratio has been achieved, the risk of developing RDS is small.[6, 12, 29] The present study demonstrated no increased frequency of neonatal RDS in infants with Rh sensitization and in those from mothers with toxemia. This is in keeping with the findings reported by others.[1, 6, 8, 13, 17, 27, 35]

There was also no increased RDS in those neonates delivered by cesarean section. Here the literature is divided, with some investigators finding an increased risk of RDS in neonates with mature L/S ratios who are delivered by cesarean section[7, 8, 15, 16] and others reporting no increased risk.[6, 10, 13] The clinician contemplating early delivery of a high-risk fetus with a mature L/S ratio apparently does not need to worry about the route of delivery (cesarean section or vaginal delivery), provided fetal hypoxia is prevented.

There appear to be some neonates at risk for RDS despite a mature L/S ratio. There have been conflicting reports as to the occurrence of RDS in infants of mothers with insulin-dependent diabetes and a mature L/S ratio. The reports of eight series with 164 patients show no neonatal RDS if the L/S ratio is mature.[4, 13, 15, 17, 21, 27, 30, 35] However, other reports have presented the occasional case of RDS after a mature L/S ratio, and these cases are summarized in Table V.[2, 6–8, 10, 16, 18–22, 26, 31–34] These reports have varied from those noting only one or two cases to reports with an incidence of 18 per cent. There have been four neonatal deaths (2.4 per cent) from hyaline membrane disease reported in this group. The present study confirms and expands these reports and presents a frequency of RDS of 28.5 per cent in infants with insulin-dependent diabetic mothers and a mature L/S ratio. However, there were no neonatal deaths secondary to hyaline membrane disease. Although these results might suggest that the present criteria for lung maturity evaluation are not adequate for infants of insulin-dependent diabetic

Table V. Reported pregnancies with diabetes mellitus and neonatal respiratory distress (RDS) despite a mature amniotic fluid L/S

Author	*Year*	*Total no. of diabetic patients*	*No. with mature L/S and RDS*	*L/S ratio*
White and associates[32]	1972	–	1	3/1
Biggs and associates[2]	1972	–	1	2.4/1
Lemons and Jaffe[18]	1973	14	2	>2/1
Gabert and associates[10]	1973	45	1*	2.6/1
Whitfield and associates[34]	1973	93 (27 gestational)	1	>2/1
Donald and associates[6]	1973	77	1*	>2/1
Wagstaff and Bromham[31]	1973	–	1	2.7/1
Dunn and associates[8]	1974	12	3*	>2/1
Meyers and associates[21]	1974	–	1	5/1
Polishuk and associates[26]	1974	20 (12 Latent)	2	>2/1
White[33]	1974	—	1	5/1
Mukherjee and associates[22]	1974	12	2	2.8/1; 2/1
Merola and associates[20]	1974	25	1	2.1/1
Keniston and associates[16]	1975	–	1	4.5/1
Duhring and Thompson[7]	1975	38	5	–
Marshall and Paris[19]	1975	–	1*	2.1/1

*Indicates one neonatal death from hyaline membrane disease.

mothers, another explanation could be that the respiratory distress of these newborn infants results from a different mechanism.[3] Such a mechanism might be fluid shifts in the respiratory center due to high blood glucose levels and altered osmotic fluid pressures. Several authors report a terminal fall in the L/S ratio in diabetic gestations.[9, 26, 34]

Another group of neonates which are at risk for RDS are those with "distress" and a resulting low Apgar score. Hobel and associates[14] first described an increased RDS frequency in neonates with abnormal heart rate patterns in labor and low Apgar scores at delivery. Donald and co-workers[6] reported an increased risk for RDS despite a mature L/S ratio in infants with low five-minute Apgar scores. The present study also shows a good correlation between a low Apgar score at both the one- and five-minute time periods and the development of RDS. Of the eight infants who developed RDS, seven had a one-minute Apgar score less than 7, and three had a five-minute Apgar score of less than 7. Hypoxia and hypothermia leading to acidosis are known to inhibit the methyl transferase enzyme system which is the predominant pathway for lecithin synthesis in premature infants.[11] Whether such a mechanism is involved in these neonates with mature lungs is not known.

The results of this study and other studies support the concept of delivering diabetic and other women who may have depressed neonates in centers where continuous biophysical and biochemical monitoring of the fetus can be performed during labor and where a contiguous neonatal intensive care unit exists so that long transport of the critically ill neonate can be avoided. This is because these infants may develop respiratory distress and/or hyaline membrane disease despite the fact that amniotic fluid indicators such as the L/S ratio show fetal lung maturity.

The authors wish to thank Drs. Rose Ray and Dennis Dixon for their help in the statistical analysis of these data.

REFERENCES

1. Bhagwanani, S. G., Fahmy, D., and Turnbull, A. C.: Prediction of neonatal respiratory distress by estimation of amniotic fluid lecithin, Lancet **1:** 159, 1972.
2. Biggs, J. S. G., Gaffney, T. J., McGeary, H. M., and McMahon, M. J.: The phospholipid test of fetal respiratory maturity: Its value in clinical obstetrics, Aust. N. Z. J. Obstet. Gynaecol. **13:** 92, 1973.
3. Boehm, F. H., Srisupundit, S., and Ishii, T.: Lecithin-sphingomyelin ratio and a rapid test for surfactant in amniotic fluid: A comparison, Obstet. Gynecol. **41:** 829, 1973.
4. Bryson, M. J., Gabert, H. A., and Stenchever, M. A.: Amniotic fluid lecithin/sphingomyelin ratio as an assessment of fetal pulmonary maturity, Am. J. Obstet. Gynecol. **114:** 208, 1972.
5. Buhi, W. C., and Spellacy, W. N.: Effects of blood or meconium on the determination of the amniotic fluid lecithin/sphingomyelin ratio, Am. J. Obstet. Gynecol. **121:** 321, 1975.
6. Donald, I. R., Freeman, R. K., Goebelsmann, U., Chan, W. C., and Nakamura, R. M.: Clinical experience with the amniotic fluid lecithin/sphingomyelin ratio, Am. J. Obstet. Gynecol. **115:** 547, 1973.
7. Duhring, J. L., and Thompson, S. A.: Amniotic fluid phospholipid analysis in normal and complicated pregnancies, Am. J. Obstet. Gynecol. **121:** 218, 1975.
8. Dunn, L. J., Bush, C., Davis, S. E., III, and Bhatnagar, A. S.: Use of laboratory and clinical factors in the management of pregnancies complicated by maternal disease, Am. J. Obstet. Gynecol. **120:** 622, 1974.
9. Dyson, D., Blake, M., and Cassady, G.: Amniotic fluid L/S ratio in complicated pregnancies, Clin. Res. **23:** 73A, 1975.
10. Gabert, H. A., Bryson, M. J., and Stenchever, M. A.: The effect of cesarean section on respiratory distress in the

presence of a mature lecithin/sphingomyelin ratio, AM. J. OBSTET. GYNECOL. **116:** 366, 1973.
11. Gluck, L., Kulovich, M. V., Borer, R. H., Jr., Brenner, P. H., Anderson, G. G., and Spellacy, W. N.: Diagnosis of the respiratory distress syndrome by amniocentesis, AM. J. OBSTET. GYNECOL. **109:** 440, 1971.
12. Gluck, L., and Kulovich, M. V.: Lecithin/sphingomeylin ratios in amniotic fluid in normal and abnormal pregnancy, AM. J. OBSTET. GYNECOL. **115:** 539, 1973.
13. Hobbins, J. C., Brock, W., Speroff, L., Anderson, G. G., and Caldwell, B.: L/S ratio in predicting pulmonary maturity in utero, Obstet. Gynecol. **39:** 660, 1972.
14. Hobel, C. J., Hyvarinen, M. A., and Oh, W.: Abnormal fetal heart rate patterns and fetal acid-base balance in low birth weight infants in relation to respiratory distress syndrome, Obstet. Gynecol. **39:** 83, 1972.
15. Kalbac, R. W., and Newman, R. L.: Amniotic fluid analysis in complicated pregnancies, Obstet. Gynecol. **44:** 814, 1974.
16. Keniston, R. C., Pernoll, M. L., Buist, N. R. M., Lyon, M., and Swanson, J. R.: A prospective evaluation of the lecithin/sphingomyelin ratio and the rapid surfactant test in relation to fetal pulmonary maturity, AM. J. OBSTET. GYNECOL. **121:** 324, 1975.
17. Kling, O. R., Crosby, W. M., and Merrill, J. A.: Amniotic fluid correlates of fetal maturity and perinatal outcome, Gynecol. Invest. **4:** 38, 1973.
18. Lemons, J. A., and Jaffe, R. B.: Amniotic fluid lecithin/sphingomyelin ratio in the diagnosis of hyaline membrane disease, AM. J. OBSTET. GYNECOL. **115:** 233, 1973.
19. Marshall, B. R., and Paris, F.: Maternal serum heat-stable alkaline phosphatase in normal and high risk pregnancies, Obstet. Gynecol. **45:** 136, 1975.
20. Merola, J. C. L., Johnson, L. M., Bolognese, R. J., and Corson, S. L.: Determination of fetal pulmonary maturity by amniotic fluid lecithin/sphingomyelin ratio and rapid shake test, AM. J. OBSTET. GYNECOL. **119:** 243, 1974.
21. Meyers, J. S., Coch, E. H., Goldman, G. M., and Kessler, G.: Amniotic fluid lecithin/sphingomyelin ratio and other tests for fetal maturity, South Med. J. **67:** 431, 1974.
22. Mukherjee, T. K., Rajegowda, B. K., Glass, L. L., Auerback, J., and Evans, H. E.: Amniotic fluid shake test versus lecithin/sphingomyelin ratio in the antenatal prediction of respiratory distress syndrome. AM. J. OBSTET. GYNECOL. **119:** 648, 1974.
23. Myers, J. L., Harrell, M. J. P., and Hill, F. L.: Fetal maturity: Biochemical analysis of amniotic fluid, AM. J. OBSTET. GYNECOL. **121:** 961, 1975.
24. Nelson, G. H., and Lawson, S. W.: Determination of amniotic fluid total phospholipid phosphorus as a test for fetal lung maturity, AM. J. OBSTET. GYNECOL. **115:** 933, 1973.
25. Nelson, G. H.: Relationship between amniotic fluid lecithin concentration and respiratory distress syndrome, AM. J. OBSTET. GYNECOL. **112:** 827, 1972.
26. Polishuk, W. Z., Anteby, S., Stein, Y., and Bar-on, H.: Lecithin/sphingomyelin ratio in amniotic fluid of diabetic and latent diabetic pregnancies, Int. J. Gynecol. Obstet. **12:** 49, 1974.
27. Schreyer, P., Tamir, I., Bukovsky, I., Weinraub, Z., and Caspi, E.: Amniotic fluid total phospholipids versus lecithin/sphingomyelin ratio in the evaluation of fetal lung maturity, AM. J. OBSTET. GYNECOL. **120:** 909, 1974.
28. Spellacy, W. N., and Buhi, W. C.: Amniotic fluid lecithin/sphingomyelin ratio as index of fetal maturity, Obstet. Gynecol. **39:** 852, 1972.
29. Spellacy, W. N., and Buhi, W. C.: The usefulness of amniotic fluid lecithin/sphingomyelin ratio in predicting neonatal respiratory problems, South Med. J. **66:** 1090, 1973.
30. Tchobroutsky, C., Cédard, L., Rouvillois, J. L., and Amieltison, C.: Le rapport lécithine-sphingomyéline au liquide amniotique dans les grossesses diabéteques insulinodepéndantes, J. Gynecol. Obstet. Biol. Reprod. **4:** 93, 1975.
31. Wagstaff, T. I., and Bromham, D. R.: A comparison between the lecithin/sphingomyelin ratio and the "shake test" for the estimation of surfactant in amniotic fluid, J. Obstet. Gynaecol. Br. Commonw. **80:** 412, 1973.
32. White, C. A., Musiala, T. S., and Witte, D. L.: Amniotic fluid lecithin/sphingomyelin ratio as a measure of fetal pulmonary maturity, J. Iowa Med. Soc. **62:** 279, 1972.
33. White, P.: Diabetes mellitus in pregnancy, Clin. Perinatol. **1:** 331, 1974.
34. Whitfield, C. R., Sproule, W. B., and Burdenell, M.: The amniotic fluid lecithin:sphingomyelin area ratio (LSAR) in pregnancies complicated by diabetes, J. Obstet. Gynaecol. Br. Commonw. **80:** 918, 1973.
35. Yareč, L. E., McGeary, H. M., and Gaffney, T. J.: The value of the amniotic fluid lecithin:sphingomyelin ratio in the management of high risk pregnancy, Aust. N. Z. J. Obstet. Gynaecol. **13:** 98, 1973.

Reported live births following induced abortion: Two and one-half years' experience in Upstate New York

GEORGE STROH*
ALAN R. HINMAN, M.D.**
Albany, New York

Thirty-eight live births following induced abortion were recorded in Upstate New York between July, 1970, and December, 1972. Twenty-six followed saline-induced abortion; twelve of these occurred at one hospital, and eight were associated with one physician. Underestimation of gestation and exchange of inadequate volumes of amniotic fluid and hypertonic saline produced concentrations insufficient to cause intrauterine death. Viable infants with iatrogenic central nervous system damage from salt poisoning are a possible consequence of improperly planned saline-induced abortions. These births provide further evidence for encouragement of contraception and early termination of unwanted pregnancy.

DELIVERY OF LIVE FETUSES following induced abortion is infrequently and passingly mentioned in the literature.[1–3] Most such deliveries produce nonviable infants who die shortly after delivery because of immaturity. Delivery of an "unharmed" fetus would most frequently be expected following procedures that do not produce in utero conditions intolerable to the fetus: hysterotomy, metreurynter, or protaglandin or other hormonal intervention.

New York law was modified to permit induced abortion through the twenty-fourth week of pregnancy beginning July 1, 1970. The State's Public Health Law requires that induced abortions, regardless of gestation, be reported to the State Health Department on a Certificate of Fetal Death.

From the Division of Epidemiology and Preventive Health Services, New York State Department of Health.

Received for publication May 27, 1975.

Revised March 4, 1976.

Accepted March 19, 1976.

Reprint requests: Family Planning Evaluation Division, (Attention: Ms. R. Kurtz), Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia 30333.

**Public Health Advisor, Family Planning Evaluation Division, Bureau of Epidemiology, Center for Disease Control (CDC), Public Health Service, United States Department of Health, Education, and Welfare. Present address: CDC Career Development Program, Columbia University School of Public Health.*

***Present address: Assistant Commissioner, Tennessee Department of Public Health, Nashville, Tennessee.*

State law defines a live birth (Public Health Law Section 4130 [1] as:

> The complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.

All live births must be registered with the Health Department with a Certificate of Birth. Thus, the presence of any evidence of life in a fetus delivered by induced abortion must be reported as a live birth. When the infant dies, filing of a Certificate of Death is required.

In early 1973, the State Health Department began an investigation of live births following induced abortion. The purpose of the investigation was to determine their incidence and the extent to which they represented a public health problem and, if possible, to formulate solutions to identifiable problems. The study was limited to events occurring in New York State exclusive of New York City (Upstate New York), because of ease of access to data. Events occurring between July 1, 1970, and December 31, 1972, in Upstate New York are the primary focus of this paper.

Material and methods

During January and February of 1973, the Office of Biostatistics of the State Health Department retrieved

Table I. Live-birth rate following induced abortion in Upstate New York: 1970 to 1972

Date	*Amniocentesis*			*Hysterotomy*			*All procedures*		
	No.	*Live births*	*Rate**	*No.*	*Live births*	*Rate**	*No.*	*Live births*	*Rate**
July-December., 1970	2,095	5	2.4	364	4	11.0	18,535	10†	0.54
January-December., 1971	5,195	12	2.3	448	2	4.5	56,134	15‡	0.27
January-December., 1972	8,381	10	1.2	252	3	11.9	76,518	13	0.17
Total	15,671	27	1.7	1,064	9	8.5	151,187	38	0.25

*Reported live births per 1,000 reported abortions.
†Includes one oxytocin-induced abortion.
‡Includes one abortion by an unknown procedure.

Certificates of Birth and Certificates of Death which indicated induced abortion was the method of delivery or a cause of death, respectively. The data obtained from the certificates were reviewed and arrangements were made to review the medical records of the mothers and infants at the hospitals from which these events were reported.

Review and analysis of the pertinent medical records indicated that live births following saline–amniotic fluid exchange were a specific problem associated with one hospital (Hospital A). Arrangements were made to review a sample of medical records for characteristics of all saline abortions done there between July 1, 1970, and December 31, 1972. Another hospital that reported live births (at a lower incidence) was also contacted, and saline abortions done there were reviewed to compare the experience with that of Hospital A.

An additional sample of saline abortions was obtained from the Joint Program for the Study of Abortion (JPSA) which was available through the Family Planning Evaluation Branch of the Center for Disease Control. A 10 per cent systematic random sample of saline abortions done in 1971 and 1972 at the 13 participating institutions was obtained, and selected characteristics were studied.*

Results

Thirty-five births following induced abortion occurred between July 1, 1970, and December 31, 1972, and were reported on birth and death certificates in Upstate New York. One additional live birth was reported for which no death certificate was filed, and subsequent investigation revealed that the infant survived. Information on two more live births was obtained during record reviews at hospitals, giving a total of 38 known live births following induced abortion during the first two and a half years of liberalized abortion. A total of 151,187 abortions was performed in Upstate New York during that period.

Table I shows the temporal distribution of the 38 births. The over-all rate of live births following abortion declined significantly over the two and a half years ($p < 0.01$). The decrease following amniocentesis is not statistically significant, although the rate in 1972 is only half as great as during the preceding one and a half years.

The characteristics of the women producing these infants were representative of all women having abortions in Upstate New York during the two and a half years; there were no significant differences in regard to age, race, marital status, parity, educational attainment, or place of residence. The one obvious characteristic of the patients was seeking abortion after the first trimester of pregnancy.

Table II shows the distributions of the 38 reported live births by gestation as recorded on the medical records, by calculation from the date of onset of the last menstrual period (LMP), and by estimation of gestation from published fetal weight-gestation tables.[4, 5]

Twenty-two (58 per cent) of the infants were male, and 16 (42 per cent) were female. Weights ranged from 280 to 1,561 grams. Seven (18 per cent) died within one hour after birth, 19 (50 per cent) died between one and four hours after birth; and 10 (26 per cent) died between four and 24 hours after delivery. Two infants (5 per cent) survived longer than 24 hours. Of the latter, one died 27 hours and 5 minutes after birth, and the other survived and was eventually discharged into the mother's care.

At least 33 (87 per cent) of the infants were given special premature infant care. Hospital records did not indicate the procedures followed for the other five (13 per cent).

Since live births would be expected more frequently with hysterotomy and some other procedures used to perform abortions in the second trimester, special attention was focused on live births following saline

*The authors are indebted to Dr. Winthrop A. Burr, Abortion Surveillance Officer, CDC, for providing the sample of JPSA abortions.

abortions as this procedure generally does not produce a living infant. Table III shows the distribution of the 27 live births following abortion by amniotic fluid exchange with saline (26) and urea (one) according to the hospital from which they were reported. After exclusion of Hospital G because of the small number of procedures, the difference in rates among the remaining eight hospitals is statistically significant ($p < 0.01$). Eight of the 12 live births which occurred at Hospital A were associated with a single physician (Physician X) who performed over half of the saline abortions at Hospital A.

Successful abortion following saline amniocentesis depends on achieving sufficient osmolarity in the amniotic fluid. Because of the relatively large birth weights and noticeably small fluid volumes exchanged in some of the saline abortions studied, amniotic fluid volumes were estimated for the 26 saline procedures which produced live births based on Fuch's[6] studies of amniotic fluid volumes at different stages of pregnancy. Subtracting the amniotic fluid withdrawn and adding the volume of saline instilled produced an estimated final amniotic sac fluid volume after amniocentesis. The concentration of NaCl in the final volume was calculated with allowance for dilution by the estimated volume of amniotic fluid remaining in the sac.

These calculations were performed with gestation measured in two different ways—from fetal weight and by date since LMP. Table IV shows the results with gestation estimated from fetal weight, and Fig. 1 (top) displays the distribution of the estimated final concentration of NaCl in the sac after amniocentesis for abortions which resulted in known live births. Table V and Fig. 1 (bottom) show data on the final NaCl concentration with amniotic fluid volume estimated by gestation from LMP data. The lower probable concentrations of NaCl achieved in the amniotic sac when gestation is estimated from fetal weights is evident.

To determine if saline abortions at Hospital A were inherently at greater risk of live births, selected data from a sample of all saline abortions not producing live births done there during the two and a half year period were obtained. Similar data were obtained at Hospital C and from the JPSA samples. Table VI shows a summary of these data (Physician X is a subset of Hospital A's data). In general, saline abortions at Hospital A (more specifically, Physician X) were associated with longer gestations and larger fetuses, with little or no amniotic fluid aspiration and smaller volumes of saline introduced. Fig. 2 shows the distribution of estimated "final" concentrations of NaCl for the three groups. The difference between the estimated "final" NaCl concentrations at Hospital A and the other two samples is obvious and statistically significant ($p < 0.001$).

Table II. Distribution of live births following induced abortion by gestation as indicated on hospital admission records, as calculated from the last menstrual period and as estimated from fetal weight in Upstate New York from July, 1970, to December, 1972

Gestation in weeks	*No. of live births by gestation*		
	From admission records	*Calculated from last menstrual period*	*Estimated from fetal weight*
<16	0	2	0
16-19	17	13	1
20-23	17	15	6
24	3	1	1
>24	1	6	28
Total	38	37*	36†

*Excludes one abortion for which last menstrual period was unknown.

†Excludes two abortions for which fetal weight was not recorded on hospital records.

Table III. Reported live-birth rate following amniocentesis for institutions reporting such events in Upstate New York from 1970 to 1972

Institution	*No. of procedures*	*No. of live births*	*Live births/ 1,000 procedures*
A	455	12	26.4
B	570	4	7.0
C	1,060	2	1.9
D	818	2	2.4
E	341	2	5.9
F	5,692	2	0.3
G	5	1	*
H	199	1	5.0
I	187	1	5.3
Total	9,327	27	2.9

*See text.

Comment

The decline in the over-all rate of live births following induced abortions over the two and a half years is related to an increasing proportion of abortions performed earlier in pregnancy. The relatively large weights of the live-born infants reported probably indicate that presumed viability was the primary consideration in the decision to report the deliveries on birth certificates rather than a strict adherence to the legal definition of life at delivery. The fact that only nine live births were reported for over a thousand hysterotomies performed lends support to this in-

Table IV. Gestation, amniotic fluid volumes, and final NaCl concentration estimated from fetal weight for 26 live births following saline-induced abortion, Upstate New York, July, 1970, through December, 1972

Case No.	Infant's Weight (grams)	Estimated gestation (wk.)	Estimated Amniotic fluid volume	Amniotic fluid aspirated	Saline infused		Estimated final amniotic sac volume	Estimated final NaCl concentration*
					Volume	Concentration		
1	851	26	675	—	150	—†	825	4.3
2	1,532	32	850	—	150	—	1,000	3.7
3	1,419	31	850	—	100	—	950	2.9
4	1,078	28	775	—	150	—	292	4.0
5	795	25	625	—	150	—	775	4.6
6	624	25	625	—	100	—	725	3.5
7	454	22	475	75	125	—	525	5.4
8	880	26	675	—	130	—	805	3.9
9	851	26	675	—	150	—	825	4.3
10	1,561	32	850	—	150	—	1,000	3.7
11	880	26	675	110	150	—	715	4.9
12	860	27	725	180	150	—	695	5.0
13	Not recorded	—	—	—	250	20	—	—
14	1,213	29	850	80	225	20	995	5.2
15	823	26	675	—	180	20	855	4.9
16	1,200	—	—	—	—	—	—	—
17	738	25	625	10	250	20	865	6.4
18	642	25	625	100	200	20	725	6.1
19	850	26	675	100	200	20	775	5.8
20	326	21	425	110	90	—	405	5.1
21	355	21	425	50	50	23.4	425	3.5
22	1,490	31	850	150	160	0.85	860	0.85
23	1,163	30	850	170	170	20	850	4.7
24	550	24	575	150	200	—	625	7.0
25	880	26	675	—	150	—	825	4.3
26	823	25	625	120	130	23.4	635	5.5

*Concentrations of NaCl calculated in per cent weight/volume.

†Indicates data were not recorded on medical records, and we assumed 20 per cent saline was used to calculate estimated final NaCl concentration.

terpretation, as live births would frequently be expected with this procedure.

Although the women to whom these live births occurred were similar as a group to other women seeking abortion in Upstate New York, they are different in that the infants delivered were larger than would normally be expected for pregnancies of 24 weeks' duration or less. The difference between gestation as obtained from the admission records and gestation estimated from fetal weight was particularly noticeable for live births following amniocentesis. Mean gestation from admission records is about six weeks less than gestation estimated from fetal weight.

Three possible explanations exist for the relatively large weights of these infants:

1. If gestation was correctly determined from the LMP history and physical examination, they could be high-weight deviants above the expected norm of about 630 grams for 24 weeks' gestation.[4]

2. It is also possible that the estimates of gestation at admission were based on erroneous information given by the patients. Some may have mistakenly given the date of the first missed menses or have had "spotting" at conception or the following missed menses. If the physician used such incorrect information, it would result in underestimation of gestation by about four weeks—an underestimating which occurs with relative frequency with term pregnancy confinement estimates.[7]

3. Some women may have waited too long to obtain a legitimate abortion "on demand" and gave an erroneous LMP history.

The number of live births following induced abortion continued to decline through 1973 (seven were reported with one survival), but, in 1974, the number increased to 15.

The two infants who survived saline abortions in Upstate New York were discharged with no evident damage from salt poisoning. Two other infants are known to have survived in New York City during the

Table V. Gestation, amniotic fluid volume, and final NaCl concentration calculated from date of LMP for 26 live births following saline-induced abortion in Upstate New York, July, 1970 to December, 1972

Case No.	Gestation calculated from LMP	Estimated amniotic fluid volume	Amniotic fluid aspirated	Saline infused		Estimated final volume	Estimated final NaCl concentration*
				Volume	Concentration		
1	24.2	575	—	150	—†	725	4.8
2	19.5	325	—	150	—	475	6.9
3	19.4	325	—	100	—	425	5.4
4	21.5	425	—	150	—	575	5.8
5	20.0	375	—	150	—	525	6.3
6	20.0	375	—	100	—	475	7.0
7	18.0	275	75	125	—	325	8.2
8	16.0	175	—	130	—	305	9.0
9	19.5	325	—	150	—	475	6.9
10	19.5	325	—	150	—	475	6.9
11	21.5	425	110	150	—	465	7.0
12	19.8	375	180	150	—	345	9.2
13	21.1	425	—	250	20	675	7.9
14	22.4	475	80	225	20	620	7.8
15	20.4	375	—	180	20	555	7.1
16	19.0	325	—	—	—	—	—
17	37.2‡	‡	10	250	20	‡	‡
18	20.5	375	100	200	20	475	8.9
19	26.5	675	100	200	20	775	5.8
20	19.8	375	110	90	—	355	5.7
21	20.0	375	50	50	23.4	375	3.9
22	23.8	575	150	160	0.85	585	0.85
23	21.7	475	170	170	20	475	7.7
24	14.4	100	150	200	—	200	20.0
25	21.1	425	—	150	—	575	5.8
26	21.0	425	120	130	23.4	435	7.6

*Concentrations of NaCl calculated as per cent weight/volume.

†Indicates data were not recorded on medical records, and we assumed 20 per cent saline was used to calculate estimated final NaCl concentration.

‡Gestation estimated on hospital admission record as 25 weeks (gestation calculated from fetal weight is also 25 weeks). Authors did not use LMP as it was obviously erroneously recorded.

Table VI. Mean values of selected characteristics of saline abortions*

	No. in sample	Gestation† (wk.)	Fetal weight (grams)	Amniotic fluid aspirated (c.c.)	Saline injected (c.c.)
JPSA, 1972	179	17.5	Not available	80	193
Hospital C	30	17.3	303 (15)	115	140
Hospital A	62	18.6	290 (41)	66 (10)	141
Physician X	31	19.1	347 (18)	0	129
Live births	26	20.4 (25)	901 (24)	108 (13)	158

*Numbers in parentheses are the numbers of hospital records on which data were recorded for each characteristic. Mean values were calculated with these numbers used as denominators.

†Calculated from last menstrual period.

first two and a half years of liberalized abortion in the state.[8]

Of the 15 live births reported in 1974, six were associated with abortion induced with prostaglandins, an increasingly used procedure for terminating unwanted pregnancy. However, the weights of the infants delivered alive in the 1974 abortions are significantly lower than the weights of infants delivered alive and reported in previous years ($p < 0.001$), which may indicate that more attention is being given to reporting and to the legal definition of live birth. Undoubtedly, emphasis given to this problem at the congressional hearings on abortion,[9] the New York State legislature's development of regulations requiring a second physi-

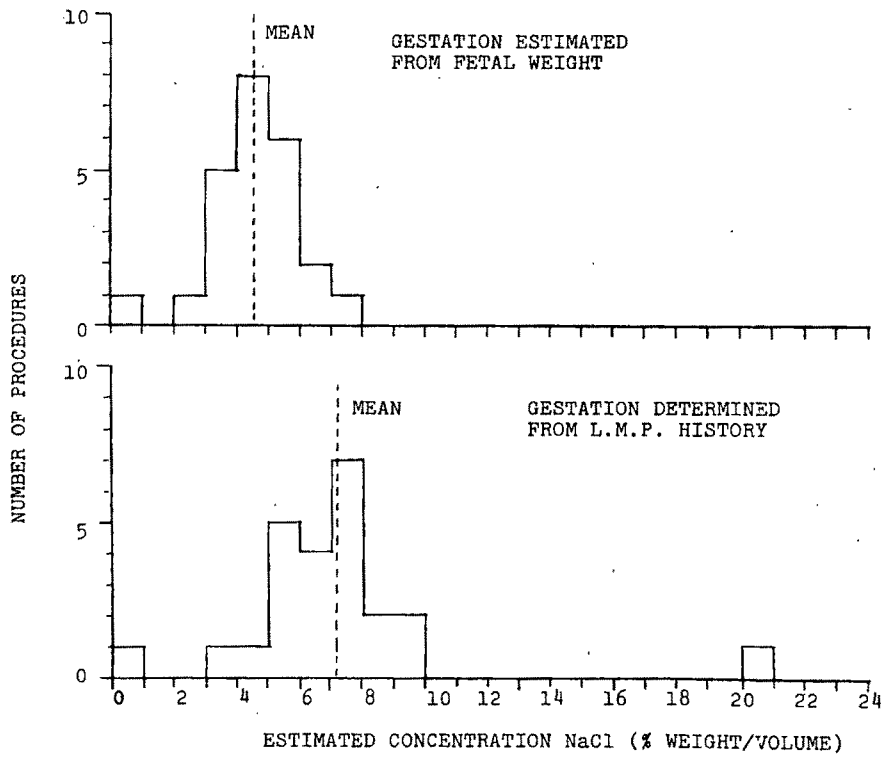


Fig. 1. Distribution of "final" NaCl concentration in 24 saline-induced abortions resulting in live births.

cian's presence at abortions after 20 weeks' gestation, and the well-publicized criminal indictments in California and Massachusetts have stimulated awareness in the medical community of such events and their possible consequences.

Saline abortion procedures as performed at Hospital A and by Physician X, in particular, have an increased risk of delivery of a live infant. Kovacs and his associates[10] reported that the time of fetal death in utero was related to the concentration of NaCl in the amniotic fluid. Longer or underestimated gestation with larger fetuses and amniotic fluid volumes can be expected to increase the dilution of NaCl injected unless larger amounts of amniotic fluid are removed. The consequent reduced NaCl concentrations produce conditions under which fetal survival can be expected to occur more frequently.

Experienced physicians recommend instillation of no more than 40 Gm. of NaCl (200 ml. of 20 per cent saline solution), since greater amounts may produce maternal hypernatremia.[11] The fetus develops hypernatremia in a saline abortion as a result of ingesting amniotic fluid[12] and by absorption through the skin. However, keratinization of fetal skin begins about the seventeenth week and is completed by about the twenty-fifth week,[13] and fetal hypernatremia is probably decreased in later abortions by the associated reduced skin permeability. Within a few hours following amniocentesis, the NaCl concentration is reduced by osmosis and fetal-maternal exchange.[14] Thus, in utero conditions producing fetal hypernatremia are continuously being reduced following the injection of hypertonic saline. Although infants born after saline amniocentesis have a low probability or survival because of immaturity, larger fetuses might be expected to survive the in utero NaCl concentrations which are rapidly being reduced during the interval between saline instillation and expulsion.

Because hypernatremia can produce osmolar insult to the central nervous sytem, irreversible brain damage might be expected to occur in some infants surviving such insult.[15]

Summary and conclusions

1. Thirty-eight live births following induced abortion are known to have occurred in Upstate New York between July 1, 1970, and December 31, 1972. Twenty-seven followed amniocentesis and nine followed hysterotomy. There was one survival.

2. A substantial portion of the live births following saline abortions were associated with one hospital and specifically with one physician.

3. In inducing abortion by saline–amniotic fluid exchange, particular attention should be given to de-

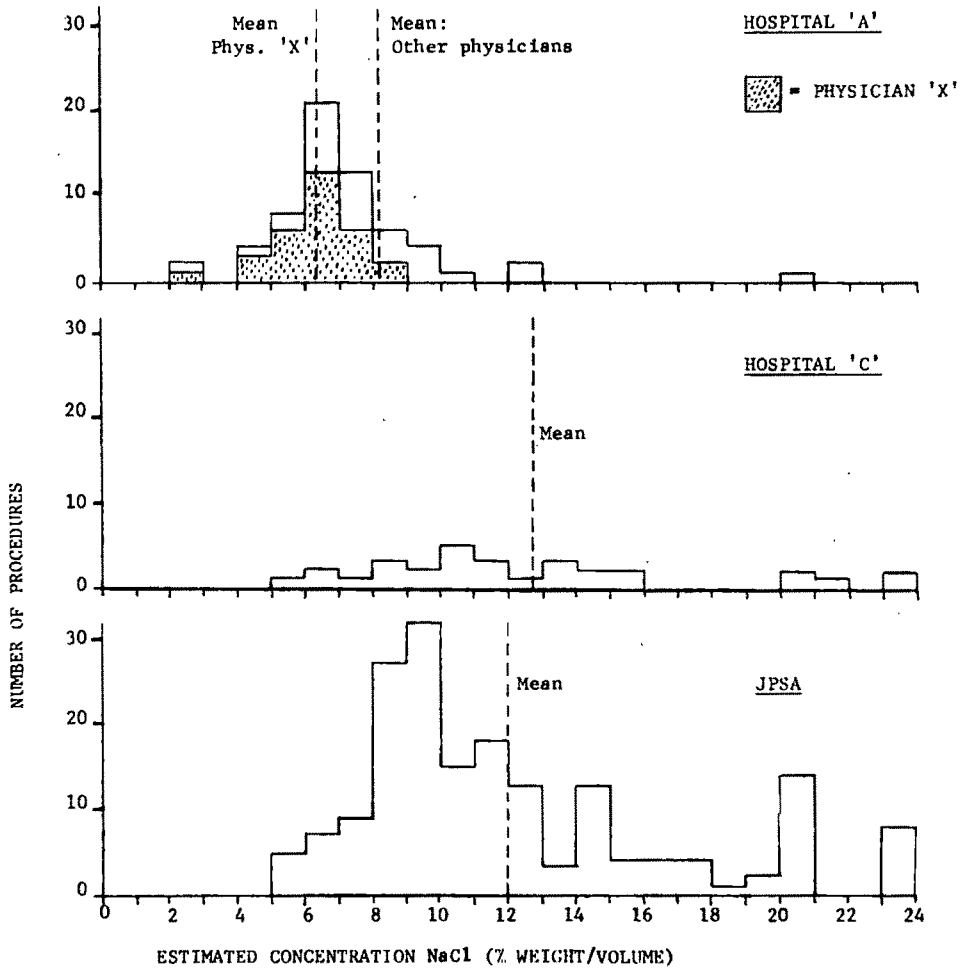


Fig. 2. Distribution of "final" NaCl concentrations in saline-induced abortions not resulting in live births for three samples: Hospital A, Hospital C, and JPSA. Gestations calculated from last menstrual period.

termining gestation, and perhaps sonography should be used in questionable instances to determine fetal size and probable amniotic fluid volume so that adequate volumes of saline and amniotic fluid are exchanged.

4. Institutions in which second-trimester abortions are performed should have adequate facilities, personnel, and procedures prepared to care adequately for the occasional live-born infant. This is now required by law in New York State.

The authors acknowledge the work of the staff of Mr. Vito Logrillo, Director of the Office of Biostatistics, New York State Department of Health, particularly Mr. Tim Smith, in retrieving the vital records pertinent to this study.

REFERENCES

1. Manabe, Y.: Artificial abortion at midpregnancy by mechanical stimulation of the uterus, AM. J. OBSTET. GYNECOL. **105:** 132, 1969.
2. Neubardt, S., and Schulman, H.: Interruption of pregnancy after twelve weeks' gestation, Saline abortion, *in* Techniques of Abortion, Boston, 1972, Little, Brown & Company, chap. 4.
3. Lauersen, N. H., and Schulman, J. D.: Oxytocin administration in mid-trimester abortions, AM. J. OBSTET. GYNECOL. **115:** 420, 1973.
4. Streeter, G. L.: Weight, sitting height, head size, foot length and menstrual age of the human embryo, Contrib. Embryol. **11:** 143, 1920.
5. Usher, R., and McLean, R.: Intrauterine growth of live-born Caucasian infants at sea level. Standards obtained from measurements in 7 dimensions of infants born

between 25 and 44 weeks of gestation, J. Pediatr. **74:** 910, 1969.
6. Fuchs, F.: Volume of amniotic fluid at various stages of pregnancy, Clin., Obstet. Gynecol. **9:** 449, 1966.
7. Gruenwald, P.: Growth of the human fetus. I. Normal growth and its variation, AM. J. OBSTET. GYNECOL. **94:** 1112, 1966.
8. Pakter, J.: Personal communication.
9. Tyler, C.: Supplement to the Statement of Carl W. Tyler, Jr., M.D., F.A.C.O.G., Before the Subcommittee on Constitutional Amendments, Senate Judiciary Committee, United States Senate. Unpublished manuscript, April, 1974.
10. Kovacs, L., et al.: The role of fetal death in the process of therapeutic abortion induced by intra-amniotic injection of hypertonic saline, J. Obstet. Gynaecol. Br. Commonw. **77:** 1132, 1970.
11. Palomaki, M. D., and Little, A. B.: Surgical management of abortion, N. Engl. J. Med. **287:** 752, 1972.
12. Wang, J. S., et al.: Body composition studies in the human fetus after intra-amniotic injection of hypertonic saline, AM. J. OBSTET. GYNECOL. **117:** 57, 1973.
13. Parmley, T. H., and Seed, A. E.: Fetal skin permeability to isotopic water (THO) in early pregnancy, AM J. OBSTET. GYNECOL. **108:** 128, 1970.
14. Kerenyi, T.: Technique of late abortion in abortion techniques and services, Amsterdam, 1972, Excerpta Medica Foundation, p. 14.
15. Macaulay, D., and Watson, M.: Hypernatremia in infants as a cause of brain damage, Arch. Dis. Child. **42:** 485, 1967.

INTERNATIONAL SYMPOSIUM ON ENDOCRINOLOGY OF THE OVARY

October 6, 7 and 8, 1976

FONDATION DE RECHERCHE EN HORMONOLOGIE
67 à 77 Boulevard Pasteur—94260 FRESNES

This meeting which groups biologists and clinicians is to present an up-to-date review of biochemical, physio-pathological and therapeutic data on the hypothalamic-pituitary-ovarian axis.

MAIN TOPICS

— Secretion of the normal ovaries
— Extra-ovarian production of sexual steroids
— Hypothalamic-pituitary-ovarian axis
— Mechanism of action of lutropin (LH)
— Hormonal regulation of the mammary development
— Hormonal patterns (with 4 lectures on menopausal women)
— Hormonal investigations in ovarian diseases

With the confirmed participation of G. E. ABRAHAM, E. E. BAULIEU, G. M. BESSER, C. P. CHANNING, B. DELIGNERES, R. G. EDWARDS, P. FRANCHIMONT, S. GELLER, J. R. GIVENS, R. B. GREENBLATT, E. GURPIDE, J. C. JOB, A. KLOPPER, M. A. KIRSCHNER, E. KNOBIL, S. G. KORENMAN, F. A. LANGLEY, B. LUNENFELD, W. J. LEMAIRE, C. LONGCOPE, V. B. MAHESH, J. M. MARSH, P. MAUVAIS-JARVIS, A. NETTER, J. P. PERSION, B. F. RICE, M. ROGER, A. V. SCHALLY, R. SCHOLLER, B. M. SHERMAN, B. TAMAOKI, R. W. TURKINGTON, A. VERMEULEN, R. VOKAER.

REGISTRATION: Dr. R. SCHOLLER,

"Symposium on Endocrinology of the Ovary"
FONDATION DE RECHERCHE EN HORMONOLOGIE
67 à 77, Boulevard Pasteur,
94260 FRESNES—FRANCE



BETADINE® Perineal Wash (concentrate) effectively deodorizes as it cleanses

BETADINE Perineal Wash, a welcome advance in personal care, thoroughly cleanses the anogenital area and, at the same time, effectively reduces or eliminates offensive odors. It contains no hexachlorophene, no irritating metallic salts...and is nonstaining and virtually nonirritating to skin and mucosa.

BETADINE Perineal Wash cleanses and deodorizes the perineum: ■ After episiotomy ■ After gynecologic, urologic and anorectal surgery ■ In the presence of incontinence or enuresis ■ In the bedridden or neurologically handicapped ■ Prior to gynecologic, obstetric and urologic examinations ■ During menstruation

Convenient Kit form: Each patient gets an individual kit—an 8 oz. bottle of BETADINE Perineal Wash Concentrate and an 8 oz. calibrated, plastic squeeze dispenser bottle for easy, efficient application.

Purdue Frederick

LABORATORIES INC.
LLVIEW AVENUE
LTO, CALIF. 94304

RICHARD G. ROGERS, PRESIDENT

YNTEX

Announcing an important new service program from Syntex --
designed specifically for the obstetrician/gynecologist

Dear Doctor:

The past two years have seen an increasing concern about the need for change and improvement in the traditional OB/GYN patient relationship.*

In seeking how we might help the specialty to maintain a close, positive relationship with women at a time of rapidly changing expectations, Syntex held a number of panel discussions with women all over the country. We asked them how they felt about their OB/GYN experiences. We got some telling answers.

We invited OB/GYNs at the Dallas ACOG meeting to listen at our booth to tapes from those panel discussions. Some 1,500 doctors, their spouses and nurses, enthusiastically took us up on that offer; you may have been one of them.

The result of those patient panels and our discussion with OB/GYNs made us realize that many of the problems of patient dissatisfaction and alienation were essentially problems in communication -- communication from the doctor and the office staff to the patient, communication from the patient to the OB/GYN team.

These problems, often minor, were producing strains in the doctor/patient relationship way out of proportion to their cause.

As a result of our research Syntex has now developed WHY PEOPLE COME BACK -- a continuing series of materials and counsel for improving communication in your practice.

Our aim was not to design an "academic" program, but one that would present practical, workable advice, forms and materials to

(over)

improve the total communication environment; a program that would cycle the experience, ideas and proven methods of OB/GYN health-care teams to their colleagues in the specialty.

We are pleased to announce the introduction of WHY PEOPLE COME BACK. We invite you to review the first materials in our on-going series when your Syntex representative calls on you. And we invite you to participate in the further development of the program, since we intend it to be responsive to the needs of practicing OB/GYNs like yourself.

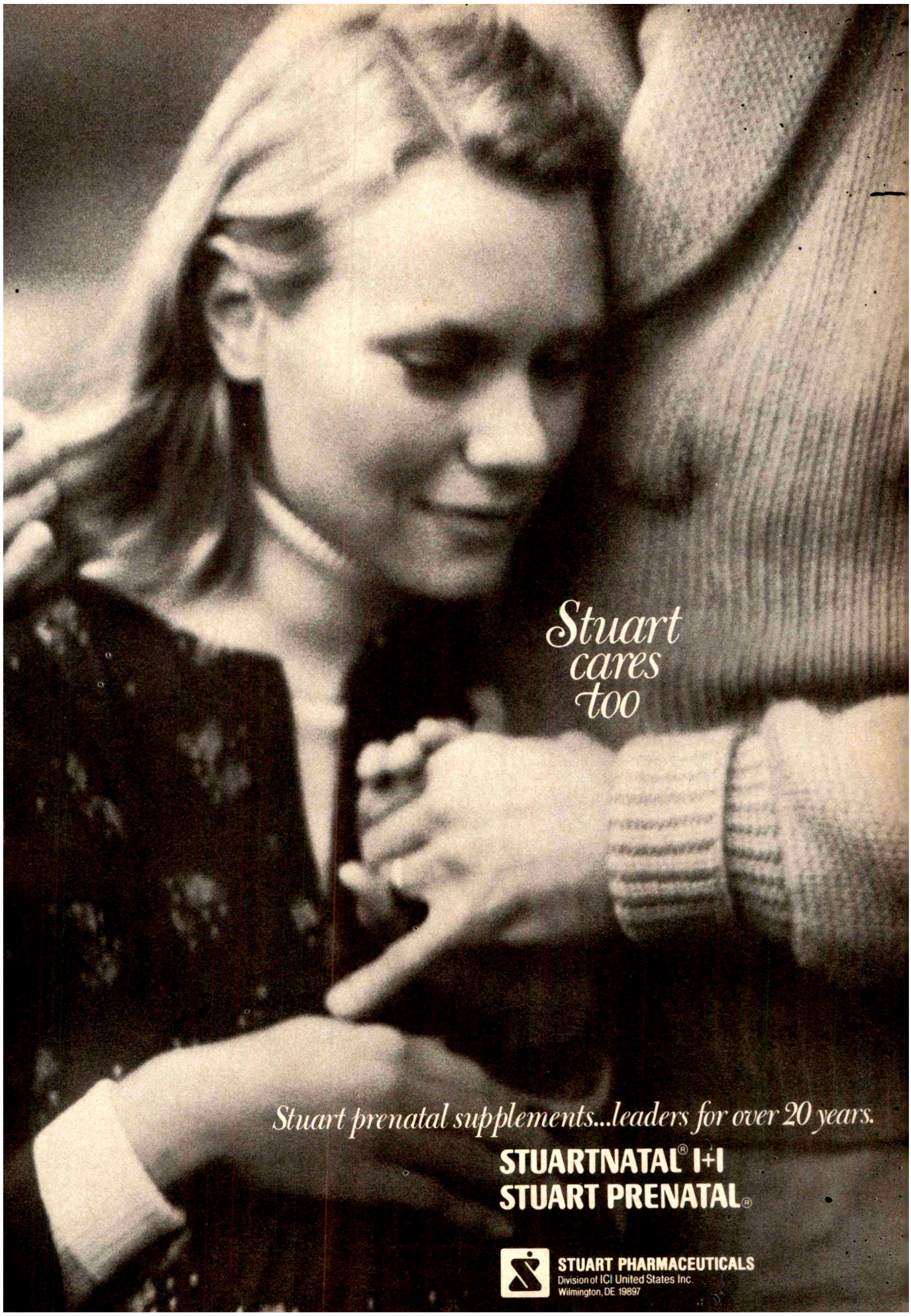
It is Syntex's privilege to serve as a communication link between OB/GYN teams and we welcome your criticism, thoughts and ideas on how we might best help you with effective communication, an important part of the art of medicine.

Sincerely,

Richard G. Rogers
President

*References:

Kaiser, B.L. and Kaiser, I.H.: Am. J. Obstet. Gynecol. 120:652, 1974.
Jorgensen, V: Obstet. Gynecol. 42:607, 1973.


Stuart
cares
too
Stuart prenatal supplements...leaders for over 20 years.
STUARTNATAL® I+I
STUART PRENATAL®
STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, DE 19897


On the OB/GYN service
Mixed infection* may not require "mixed therapy"
for anaerobic infection
for gram-negative aerobic infection
*due to susceptible strains of indicated organisms

GEOPEN® IM/IV

(DISODIUM CARBENICILLIN)

1-gm, 2-gm, 5-gm, and 10-gm vials

for treatment of infections due to anaerobes* and gram-negative aerobes* with *one* antibiotic

*susceptible strains of indicated organisms

Indications: Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa, Proteus* species (particularly indole-positive strains), and certain *Escherichia coli.* Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Severe systemic infections and septicemia; genitourinary tract infections including those due to *Neisseria gonorrhoeae, Enterobacter,* and *Streptococcus faecalis* (enterococcus); acute and chronic respiratory infections (though clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft-tissue infections. Also indicated in the following infections due to susceptible anaerobic bacteria: Septicemia; lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis; skin and soft-tissue infections.

Although indicated primarily in gram-negative infections, activity against gram-positive organisms should be kept in mind when both gram-positive and gram-negative organisms are isolated (see **Actions**).

In infections due to certain susceptible strains of *Ps. aeruginosa,* clinical efficacy may be enhanced by combined therapy with gentamicin sulfate in full therapeutic dosages (see gentamicin sulfate package insert).

NOTE: During therapy sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms.

Actions: Organisms found to be susceptible *in vitro* include: GRAM-NEGATIVE ORGANISMS—*Ps. aeruginosa, Proteus mirabilis, Pr. morgani, Pr. rettgeri, Pr. vulgaris, E. coli, Enterobacter* spp, *Salmonella* spp, *Hemophilus influenzae, Neisseria* spp, *Bacteroides* spp, and *Fusobacterium* spp.

GRAM-POSITIVE ORGANISMS—*Staphylococcus aureus* (non-penicillinase producing), *Staph. albus, Diplococcus pneumoniae,* beta-hemolytic streptococci, *Str. faecalis, Clostridium* spp, *Peptococcus* spp, and *Peptostreptococcus* spp.

In vitro synergism between Geopen and gentamicin sulfate has been demonstrated for certain strains of *Ps. aeruginosa.*

Some newly emerging pathogenic strains of *Herellea, Mima, Citrobacter,* and *Serratia* have also shown *in vitro* susceptibility.

Not stable in the presence of penicillinase. Most *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly.

Contraindications: Known penicillin allergy.

Warnings: Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations; if bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy.

Individuals with history of penicillin hypersensitivity reactions have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of carbenicillin therapy considered, unless the infection is life threatening and only amenable to carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Precautions: As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* spp and *Serratia* spp, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. In a few patients receiving high doses, hypokalemia has been reported; periodic serum potassium determinations should be made and corrective measures should be implemented when necessary. As with any penicillin preparation, an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. Cases of gonorrhea with a suspected primary lesion of syphilis should have darkfield examinations before treatment. In all other cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. Intravenous infusion should be given as slowly as possible. Reconstituted solution should be discarded after 24 hours if stored at room temperature, after 72 hours if refrigerated. The maximum recommended dose is 40 gm per day; intramuscular injections should not exceed 2 gm per injection.

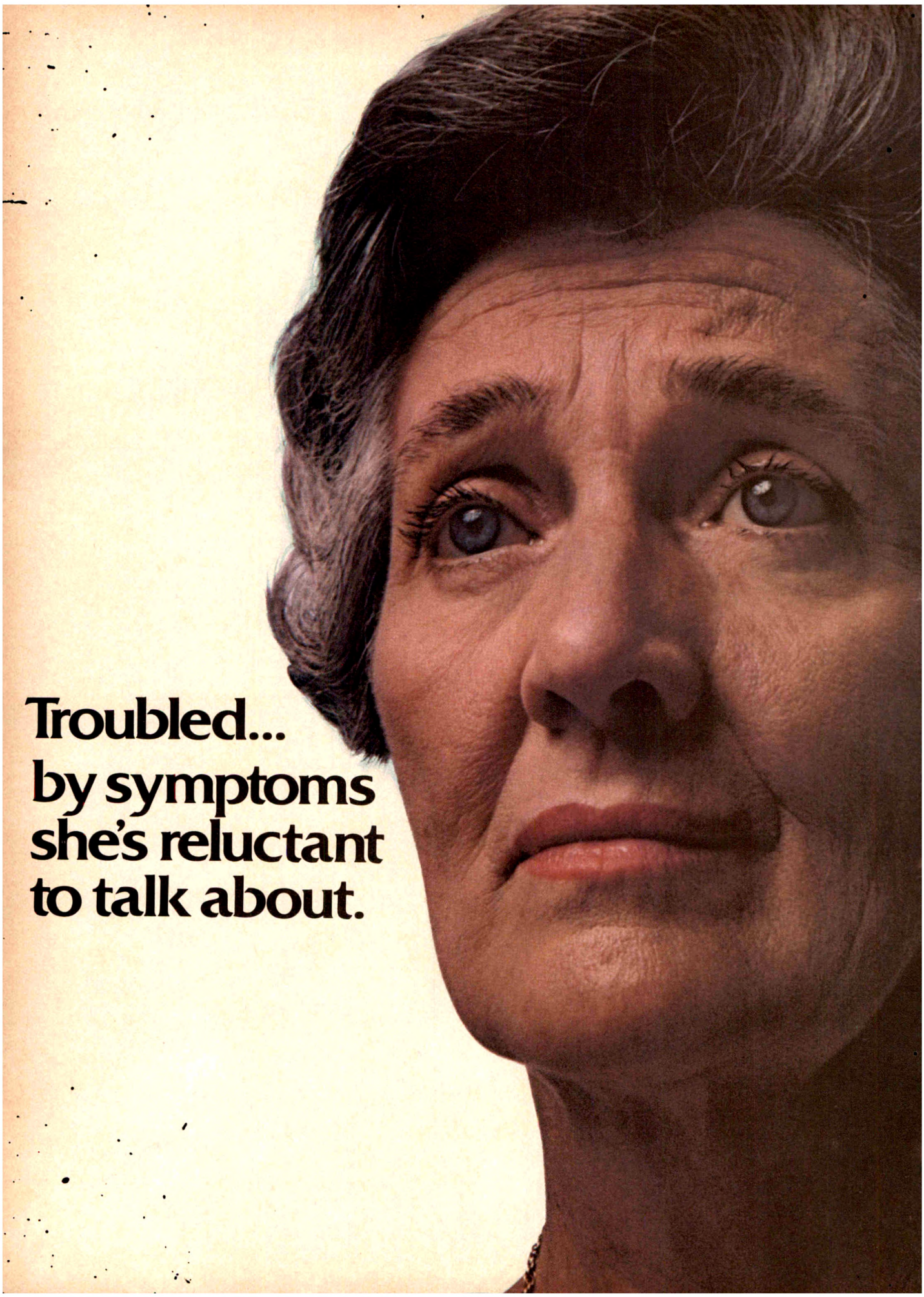


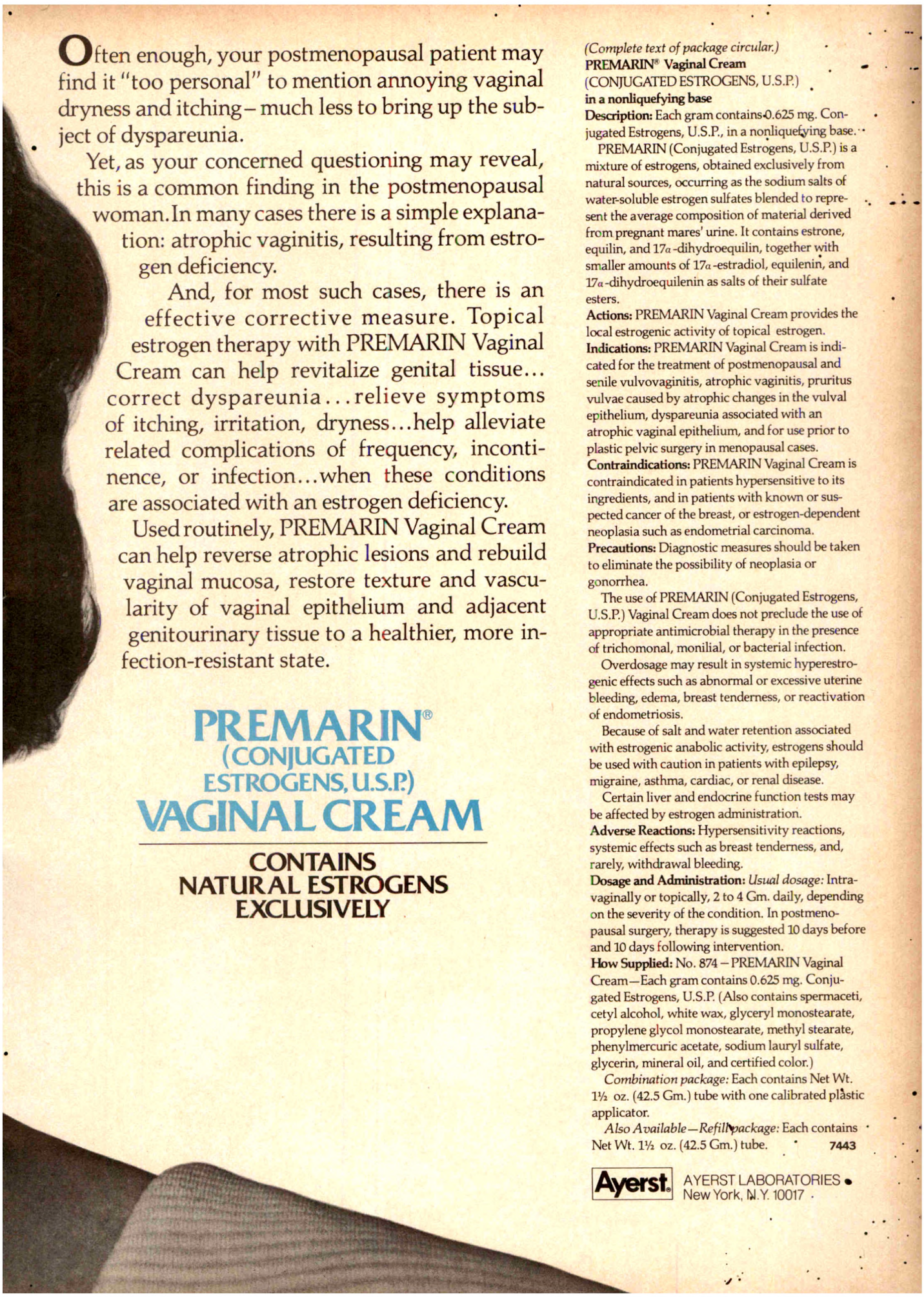
Adverse Reactions: *Hypersensitivity Reactions*—Skin rashes, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*—Nausea. *Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia. *Blood, Hepatic, and Renal Studies*—SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of hepatic or renal disorders have been demonstrated. CNS—Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Other*—Pain at the site of injection, rarely accompanied by induration; in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Vein Irritation and Phlebitis*—Particularly when undiluted solution is injected directly into the vein.

How Supplied: Available in 1-gm, 2-gm, 5-gm, and 10-gm vials.

Before prescribing or administering, see package circular or PDR.

ROERIG Pfizer A division of Pfizer Pharmaceuticals New York, New York 10017


Troubled...
by symptoms
she's reluctant
to talk about.



Often enough, your postmenopausal patient may find it "too personal" to mention annoying vaginal dryness and itching – much less to bring up the subject of dyspareunia.

Yet, as your concerned questioning may reveal, this is a common finding in the postmenopausal woman. In many cases there is a simple explanation: atrophic vaginitis, resulting from estrogen deficiency.

And, for most such cases, there is an effective corrective measure. Topical estrogen therapy with PREMARIN Vaginal Cream can help revitalize genital tissue... correct dyspareunia...relieve symptoms of itching, irritation, dryness...help alleviate related complications of frequency, incontinence, or infection...when these conditions are associated with an estrogen deficiency.

Used routinely, PREMARIN Vaginal Cream can help reverse atrophic lesions and rebuild vaginal mucosa, restore texture and vascularity of vaginal epithelium and adjacent genitourinary tissue to a healthier, more infection-resistant state.

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.)
VAGINAL CREAM

CONTAINS NATURAL ESTROGENS EXCLUSIVELY

(Complete text of package circular.)

PREMARIN® Vaginal Cream
(CONJUGATED ESTROGENS, U.S.P.)
in a nonliquefying base

Description: Each gram contains 0.625 mg. Conjugated Estrogens, U.S.P., in a nonliquefying base.

PREMARIN (Conjugated Estrogens, U.S.P.) is a mixture of estrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

Actions: PREMARIN Vaginal Cream provides the local estrogenic activity of topical estrogen.

Indications: PREMARIN Vaginal Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

Contraindications: PREMARIN Vaginal Cream is contraindicated in patients hypersensitive to its ingredients, and in patients with known or suspected cancer of the breast, or estrogen-dependent neoplasia such as endometrial carcinoma.

Precautions: Diagnostic measures should be taken to eliminate the possibility of neoplasia or gonorrhea.

The use of PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream does not preclude the use of appropriate antimicrobial therapy in the presence of trichomonal, monilial, or bacterial infection.

Overdosage may result in systemic hyperestrogenic effects such as abnormal or excessive uterine bleeding, edema, breast tenderness, or reactivation of endometriosis.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Certain liver and endocrine function tests may be affected by estrogen administration.

Adverse Reactions: Hypersensitivity reactions, systemic effects such as breast tenderness, and, rarely, withdrawal bleeding.

Dosage and Administration: *Usual dosage:* Intravaginally or topically, 2 to 4 Gm. daily, depending on the severity of the condition. In postmenopausal surgery, therapy is suggested 10 days before and 10 days following intervention.

How Supplied: No. 874 – PREMARIN Vaginal Cream—Each gram contains 0.625 mg. Conjugated Estrogens, U.S.P. (Also contains spermaceti, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylmercuric acetate, sodium lauryl sulfate, glycerin, mineral oil, and certified color.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 Gm.) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 Gm.) tube. **7443**

Ayerst AYERST LABORATORIES • New York, N.Y. 10017


©Ortho Pharmaceutical Corporation, 1976


Most women
who start with it
stay with it
Ortho-Novum 1/50
TRADEMARK
□21 and 28
Each yellow tablet contains 1 mg norethindrone and 0.05 mg mestranol. Each green tablet in the 28-day regimen contains inert ingredients.
Effective low hormonal dosage
Each tablet contains a low dosage of progestin, 1 mg norethindrone, and a low dosage of estrogen, 0.05 mg mestranol. Clinical stud th Ortho-Novum 1/50 show a pregnancy rate of only 0.26 per 100 woman years.
Low incidence of minor side effects
Experience shows a low incidence of discontinuance due to medication. Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboebolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.
Dialpak* Tablet Dispenser
Designed for your patients' convenience, but more importantly, helps reduce the possibility of error through missed tablets. The unique DIALPAK dispensing system is patient preferred.†
Please see prescribing information on next page.
*TRADEMARK †Burke Marketing Research, Inc.

Most women who start with it stay with it



Ortho-Novum 1/50 TRADEMARK □21 and 28

Ortho-Novum 1/50 □21 and Ortho-Novum 1/50 □28

Description: Each ORTHO-NOVUM 1/50 □21 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol.

Each yellow ORTHO-NOVUM 1/50 □28 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol. Each green tablet contains inert ingredients.

Actions: ORTHO-NOVUM 1/50 □21 and ORTHO-NOVUM 1/50 □28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/50 □21 and ORTHO-NOVUM 1/50 □28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28. Therefore, if such tests are abnormal in a patient taking ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 may mask the onset of the climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during ORTHO-NOVUM 1/50 □21 or ORTHO-NOVUM 1/50 □28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol-extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health, 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.I.; Vessey, M.P.; Thorogood, M.; Doll, R.; Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:241-245, May 3, 1975. **12.** Mann, J.I.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J.J.; Nora, A.H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291*(14):697-700, Oct. 3, 1974.

Ortho Pharmaceutical Corporation • Raritan, New Jersey 08869

OJ 125-6

GYNECOLOGY

Ovarian morphology in women with anosmia and hypogonadotropic hypogonadism

R. L. GOLDENBERG
R. D. POWELL
SAUL W. ROSEN
JOHN R. MARSHALL*
G. T. ROSS
Bethesda, Maryland

Ovarian biopsies from five women with the syndrome of hypogonadotropic hypogonadism and anosmia who had not previously received exogenous gonadotropins were evaluated with special emphasis on follicular morphology. Follicular development past the primordial stage was rarely observed, suggesting that early stages of follicular maturation require amounts of gonadotropins in excess of those secreted in these women.

A SYNDROME OF hypogonadism and anosmia affecting men more commonly than women and occurring in familial clusters was described by Kallman and associates[1] in 1944. The syndrome has also been called olfactogenital dysplasia,[2] and, in the limited number of women with this disorder described in the literature, primary amenorrhea was the usual basis for seeking medical care. To our knowledge, there are only three reports of ovarian follicular morphology in women with olfactogenital dysplasia who had not received exogenous gonadotropins prior to biopsy.[2–4] We have performed ovarian biopsies in the course of diagnostic evaluation of five previously untreated women presenting with primary amenorrhea, anosmia, and hypogonadotropic hypogonadism and now report our findings to add to the limited information on ovarian morphology in this syndrome.

From the Reproduction Research Branch, National Institute of Child Health and Human Development, the Laboratory of Pathology, National Cancer Institute, and the Clinical Endocrinology Branch, National Institute of Arthritis, Metabolic and Digestive Diseases, National Institutes of Health.

Received for publication December 8, 1975.

Accepted February 24, 1976.

Reprint requests: Dr. G. T. Ross, Deputy Director, The Clinical Center, National Institutes of Health, Bethesda, Maryland 20014.

**Present address: Harbor General Hospital, Torrance, California.*

Methods and results

Table I presents pertinent clinical and laboratory data on the five anosmic patients. All patients were greater than 64 inches in height, and lower-segment length was greater than upper-segment length in all of them. None had fully matured secondary sexual characteristics, although all had phenotypically normal immature female internal and external genitals. Skull x-rays and visual field examinations were normal in all patients. The buccal smear was chromatin positive, and a 46,XX karyotype was found in cells from peripheral blood cultures. Urinary 17-ketosteroid and hydroxycorticoid excretion and serum protein-bound iodine tests were within normal limits in all five sub-

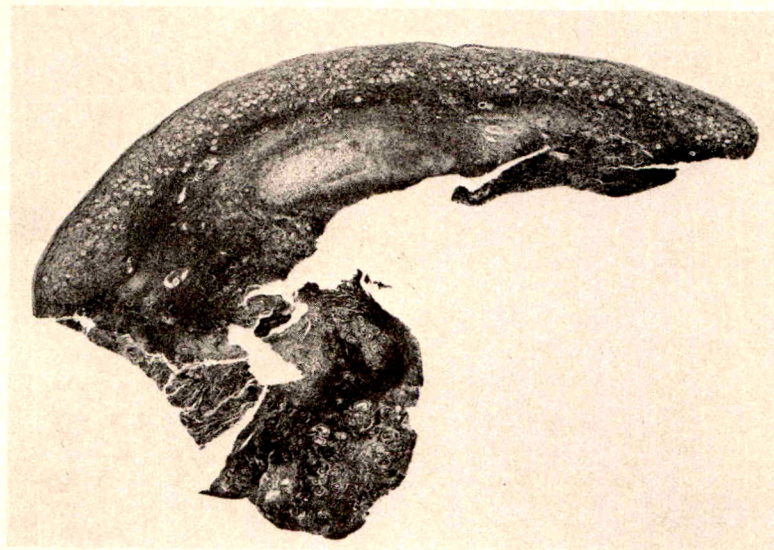


Fig. 1A. Section of ovarian biopsy from Case 2. The smooth surface, thin tunica albuginea, and large number of oocytes all suggest ovarian immaturity. Neither mature nor involuting corpora lutea are present. Except for a single atretic follicle, there is no evidence of follicle maturation beyond primary or primordial follicles. (Hematoxylin and eosin. Original magnification ×20.)

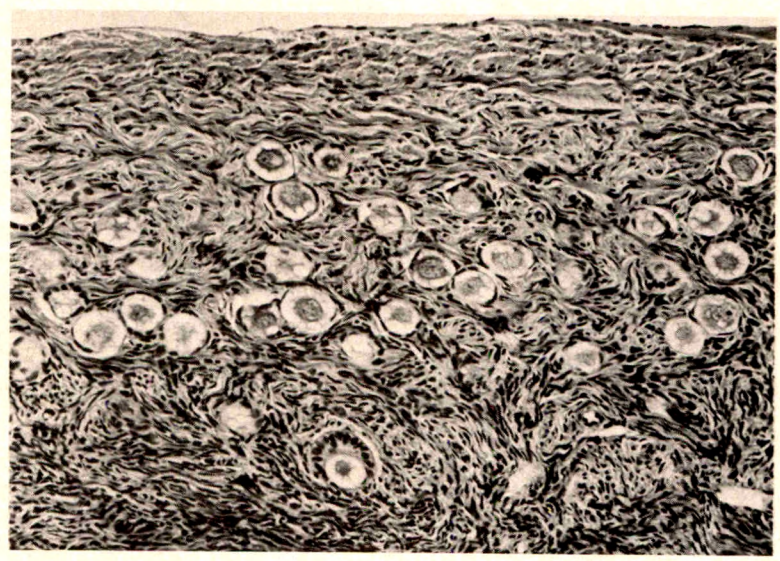


Fig. 1B. Higher power view of same section. Both primordial and primary follicles are seen, but no antral follicles are present. (Hematoxylin and eosin. Original magnification ×160.)

jects. Basal levels and response to provocative testing for growth hormone[6] were normal in the three patients tested. Cytologic examination of vaginal smears showed evidence of marked estrogen deprivation in all five patients. Total urinary gonadotropins were below the limits of detection by a mouse uterine weight assay[7] in every 24 hour urine specimen assayed in all five patients, and plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations were consistently below normal levels by the radioimmunoassay methods used in our laboratory.[8, 9] Except for anosmia, the eunuchoidal habitus, absence of secondary sexual development, and low serum and urinary gonadotropins, there were no other physical or endocrinologic abnormalities.

Culdoscopic examination and ovarian biopsy were performed on each woman.[10] The appearance of the ovary at culdoscopy and the microscopic features of the

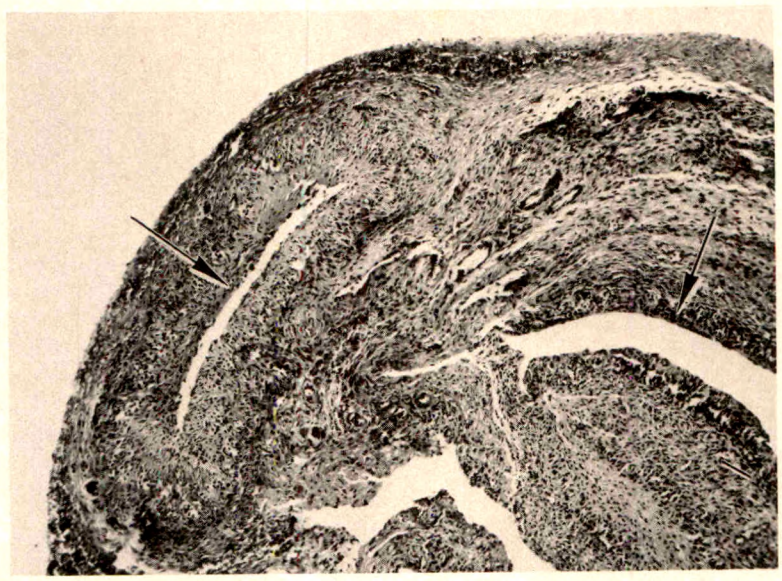


Fig. 2. Section of biopsy of right ovary from Case 2. Arrows indicate two cleftlike structures interpreted as involuting follicles. The involuting follicle to the right is in a relatively early stage of involution. (Hematoxylin and eosin. Original magnification ×80.)

Table I. Clinical and laboratory data in five patients with primary amenorrhea and anosmia

Case No.	*Age of patient (years)*	*Height (inches)*	*Lower segment (inches)*	*Karyopycnotic index in vaginal smear*	*Total urinary gonadotropins (m.u.u.*)*	*Plasma FSH (mI.U./ml.†)*	*Plasma LH (mI.U./ml.†)*
1	18	67	35	0%	<10 (×3)	3.9	5.6
2	19	64	35	0%	<10 (×6)	Not evaluated	Not evaluted
3	20	66	38	2%	<10 (×3)	<5 (×3)	<6 (×3)
4	24	69	36	1%	<10 (×5)	<4 (×10)	<6 (×10)
5	25	66	35	0%	<10 (×3)	<3 (×2)	<3 (×2)

*Mouse uterine units. In this assay 10 m.u.u. represents the lower limit of detection of gonadotropin activity in a 24 hour urine sample.

†Milli–International Units, relative to the Second International Reference Preparation. In these assays, 1 mI.U. is equivalent to 3.9 ng. of Reference Preparation LER 907 for hLH and to 30 ng. for hFSH.

Table II. Culdoscopic appearance and microscopic features of ovarian biopsies in five women with primary amenorrhea and anosmia

Case no.	*Culdoscopic appearance*	*Microscopic features*
1	1 by 1½ cm., oval, without evidence of follicles	Clusters of primordial follicles near tunica albuginea
2	Small, round , smooth capsule	Dense clusters of primordial follicles, one follicle with a single layer of cuboidal granulosa cells surrounding ovum, several involving cystic follicles
3	1 by 1 by 2 cm. with smooth capsule	Dense clusters of primordial follicles near the tunica albuginea
4	2 by 1 cm. without evidence of follicles	Dense clusters of primordial follicles near the tunica albuginea, one corpus fibrosum and several involuting cystic follicles deep in stroma
5	Small, oval without evidence of follicles	Scattered primordial follicles; one follicle with two layers of cuboidal granulosa cells

biopsy specimens are described in Table II. All ovaries were small and oval and had a smooth capsule without visible follicles.

Histologically, the ovaries appeared immature for the chronologic age of the patient. In each biopsy, primordial follicles were densely clustered in close proximity to a thin tunica albuginea (Figs. 1A and 1B). There were very few developing follicles. Occasional

involuting cystic follicles were noted (Fig. 2), but there were neither corpora lutea nor corpora albicantia to indicate previous ovulation. The presence of follicles supported the diagnosis of hypogonadotropic hypogonadism. Histologic findings in these patients are similar to those reported previously.[2–4]

Comment

In patients with primary amenorrhea and anosmia, the findings of low gonadotropin levels in serum and urine, absence of other endocrinologic abnormalities, and presence of normal but immature ovaries suggest that the hypogonadism is the result of an isolated deficiency of gonadotropins. Induction of ovulation with exogenous gonadotropins in similar patients[11, 12] gives further evidence that the defect lies not in the ovary but in the hypothalamic-pituitary unit. Both the number maturing and the extent of maturation of individual follicles were limited prior to treatment with gonadotropins. These findings and the occurrence of ovulation after treatment suggest that both preantral and postantral follicle maturation is dependent upon adequate gonadotropin stimulation.

REFERENCES

1. Kallman, F., Schonfeld, W. A., and Barrera, S. E.: Am. J. Ment. Defic. **48:** 203, 1944.
2. Gautheir, G.: Acta Neuroveg. **21:** 345, 1960.
3. Muller, P.: Gynaecologia **158:** 137, 1964.
4. Sparkes, R. S., Simpson, R. W., and Paulsen, C. A.: Arch. Intern. Med. **121:** 534, 1968.
5. Greulich, W. W., and Pyle, S. L.: *In* Radiographic Atlas of Skeletal Development of the Hand and Wrist, Stanford, California, 1955, Stanford University Press.
6. Hembree, W. C., and Ross, G. T.: Lancet **1:** 52, 1969.
7. Ross, G. T., Brice, J., and Reid, R.: *In* Sunderman, F. W., and Sunderman, F. W., Jr., editors: Laboratory Diagnosis of Endocrine Disease, St. Louis, 1971, Warren H. Green, Inc., p. 148.
8. Odell, W. D., Ross, G. T., and Rayford, P.: J. Clin. Invest. **46:** 248, 1967.
9. Cargille, C. M., Ross, G. T., and Yoshimi, T.: J. Clin. Endocrinol. Metab. **29:** 12, 1969.
10. Marshall, J. R., and Hammond, C. B.: Am. J. Obstet. Gynecol. **96:** 1022, 1966.
11. Mroueh, A., and Kase, N.: Am. J. Obstet. Gynecol. **100:** 525, 1968.
12. Tagatz, G., Fialkow, P. J., Smith, D., and Spadoni, L.: N. Engl. J. Med. **283:** 1326, 1970.

Excision of submucus fibroids with hysteroscopic control

ROBERT S. NEUWIRTH, M.D.
HUSSEIN K. AMIN, M.D.
New York, New York

Hysteroscopy offers a new option in the diagnosis and management of submucus fibroids. The hysteroscopic excision of submucus fibroids in five cases is described. The problems and potentials of this approach are discussed.

THE SUBMUCUS FIBROID is one of the more serious forms of leiomyomas of the uterus causing menorrhagia and secondary anemia, recurrent abortion, or infertility. The symptomatology usually requires operation which classically has been abdominal hysterotomy and myomectomy, or hysterectomy. Occasionally, a pedunculated submucus myoma, presenting at the cervix or in the vagina, is excised transvaginally through the dilated cervix or via vaginal hysterotomy.[1] Norment and associates[2] reported a modification of the hysteroscope to accomplish hysteroscopic resection of submucus fibroids but did not report their experiences.

The transcervical route for removal of submucus fibroids would be preferable, particularly in the younger patient who desires to preserve reproductive function, because of the avoidance of laparotomy and hysterotomy. The inability to visualize the endometrial cavity has heretofore been the major obstacle to transcervical removal of these fibroids. The tumors can be difficult to manipulate blindly for removal through the cervix. Moreover, there has been no means of visualization of the base of the tumor for appraisal of the risk of bleeding, and there has not been a sure method, short of hysterectomy, for its control should hemorrhage occur. Thus, without visual control, the hazards of a blind operation outweigh any possible advantage to transcervical removal. Hysteroscopy has provided a means of visual appraisal of the endometrial cavity and, therefore, introduces the possibility of safe excision of these tumors.[3]

In this report, the removal of submucus fibroids transcervically with hysteroscopic control in five patients is described. Although the number is small, these cases serve to illustrate the potential as well as the limitations of this application of hysteroscopy.

From the Woman's Hospital Division, St. Luke's Hospital Center, and the Department of Obstetrics-Gynecology, College of Physicians & Surgeons, Columbia University.

Financial assistance in the publication of the color photographs was provided by Pharmacia Laboratories, Inc., 800 Centennial Ave., Piscataway, New Jersey 08854.

Received for publication January 5, 1976.

Accepted January 17, 1976.

Reprint requests: Dr. Robert S. Neuwirth, Department of Obstetrics and Gynecology—Woman's Hospital, St. Luke's Hospital Center, 114th St. and Amsterdam Ave., New York, New York 10025.

Material and methods

All procedures were done in the operating room with general anesthesia. A standard hysteroscope of the Storz or ACMI type was used. Thirty-two per cent dextran 70 was used for distending the uterine cavity in four cases and 5 per cent dextrose in water was used in one case. A regular light source of 150 watts was used. For photography, a 500 watt light source, a photohysteroscope, and an Olympus SLR 35 mm. camera, or a Beaulieu 16 mm. motion picture camera, with Ektachrome ASA 160 film, were used.

Case reports

Case No. 1. Mrs. G. Q., a 26-year-old-woman, gravida 4, para 1, abortuses 3, presented with secondary infertility of three years' duration, dysmenorrhea, and a uterine filling defect on hysterography. Hysteroscopy confirmed the presence of a pendunculated fibroid. Its pedicle was cut with scissors and, although the tumor was believed to be free in the uterine cavity, it could not be extricated through the cervix because of difficulty in grasping it with an ovum forceps, the only available accessory instrument. The fibroid was subsequently removed via an abdominal hysterotomy. The postoperative course was uneventful, and the patient was discharged on the seventh postoperative day. This patient then became pregnant and was delivered of her infant by cesarean section 11 months after myomectomy.

Case No. 2. Mrs. J. E., a 32-year-old woman, who had never been pregnant, underwent dilatation and curet-

tage for heavy periods and anemia. The uterus was normal in size and measured 3½ inches. Exploration of the uterine cavity, with both ovum forceps and curet, revealed only slight irregularity on the posterior uterine wall. The curettings showed proliferative endometrium. Uterine bleeding recurred, and a hysterogram 10 months later suggested two submucosal fibroids. Hysteroscopy confirmed the presence of two pedunculated submucus fibroids. With laparoscopic and hysteroscopic control, the fibroids were morcellated by diathermic cutting, and their bases were cauterized. Postoperatively, the patient was given antibiotics and estrogens prophylactically. Recovery was uneventful with discharge on the third postoperative day. Menses have since been normal, and the anemia was corrected. The hysterogram returned to normal.

Case No. 3. Mrs. M. K., a 44-year-old woman, who had never been pregnant, was given hormonal therapy for progressive polymenorrhea, menorrhagia, and anemia. The uterus was normal, and a Papanicolaou smear and endometrial biopsy were negative for malignancy. Despite the therapeutic trial, menses continued to be heavy. At hysteroscopy, a broad-based, pedunculated, submucus fibroid, measuring 2 by 2 by 5 cm. was discovered (Figs. 1 and 2). With hysteroscopic control, morcellation by diathermic cutting was attempted but was discontinued because the instrument was too small to morcellate the tumor satisfactorily. The fibroid was then removed by grasping it with an ovum forceps, placed alongside the hysteroscope, so that the tumor was held under visual control and twisted off (Fig. 3). The pedicle was then visualized, and bleeding was controlled with light cautery. Postoperatively, the patient did well; she was treated with prophylactic estrogens and antibiotics and was discharged on the second postoperative day. The menstrual periods and blood parameters have returned to normal.

Case No. 4. Mrs. F. W., a 64-year-old, obese, hypertensive, and diabetic woman, presented with postmenopausal bleeding. Atrophic changes of the vulva and vagina and a large cervical polyp were found on examination. A Papanicolaou smear was negative. Dilatation and curettage and cervical polypectomy were performed. The uterine cavity was described as irregular, and the histology was benign. Light vaginal bleeding persisted, and a second Papanicolaou smear was negative. Six months later, a pedunculated submucus fibroid, 3 by 3 by 5 cm., was discovered at hysteroscopy. The cervix was dilated to 12 mm. which permitted the fibroid to be grasped with ovum forceps and then twisted off the pedicle. Bleeding ensued, and, though its source could be visualized, attempts at controlling it with cautery were not successful, although the uterine cavity was intact on hysteroscopic examination. One-inch iodoform gauze packing was used to control the bleeding. Packing was removed 12 hours later; the patient's recovery was uneventful, and there has been no recurrence of bleeding to date. The pathology revealed a benign leiomyoma.

Case No. 5. A 32-year-old woman, gravida 3, para 1, abortuses 2, was referred with progressive menorrhagia of one year's duration. An infertility work-up had been done, including ovulatory temperature charts. A hysterogram showed two filling defects. There was associated anemia for which the patient was receiving iron. The Papanicolaou smear was Class 1. The uterus was of normal size.

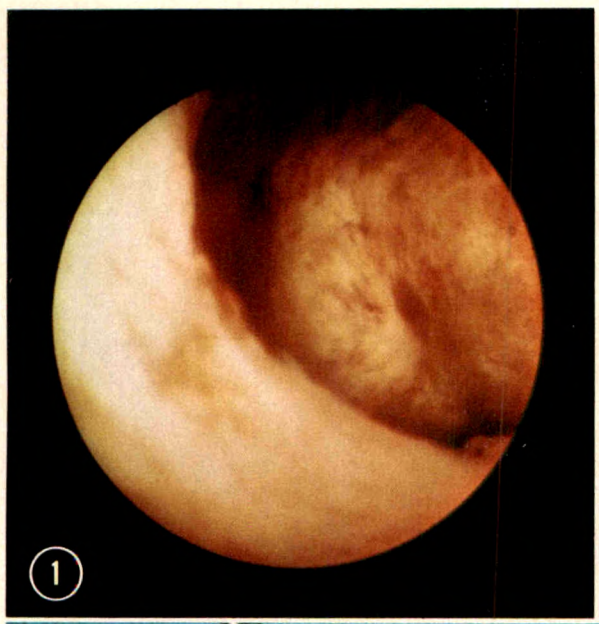
Hysteroscopic examination in the office confirmed the presence of two submucus fibroids which were believed to be amenable to hysteroscopic resection (Fig. 4). The patient was admitted and prepared for hysteroscopy, laparoscopy, and possible laparotomy. At hysteroscopy, one submucus fibroid was grasped with an ovum forceps and twisted off. The larger fibroid was morcellated with a cutting loop and removed piecemeal (Fig. 5). The estimated blood loss was less than 100 ml. Postoperatively, the patient was treated with estrogen, antibiotics, and iron. She was discharged after 48 hours. Two months later, the anemia was corrected, menses returned to normal, and a hysterosalpingogram was unremarkable. The pathology confirmed the diagnosis of uterine leiomyomas.

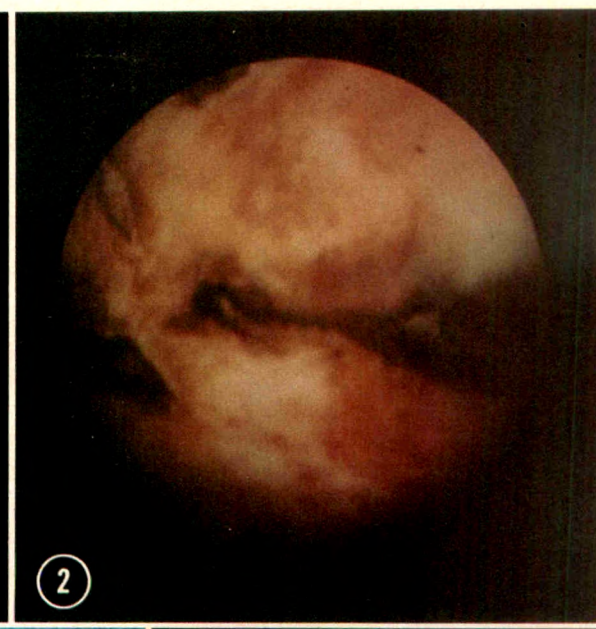
Comment

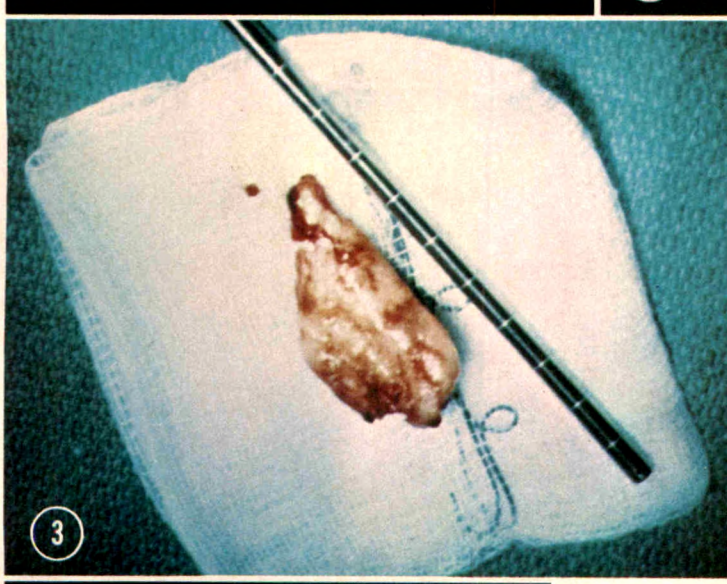
Hysteroscopy can assist in the management of abnormal vaginal bleeding associated with submucus fibroids in two ways. First, it permits precise evaluation of the endometrial cavity, thus confirming the presence of the fibroid. It also enables appraisal for the best approach to removal, including possible transcervical resection of the tumors.

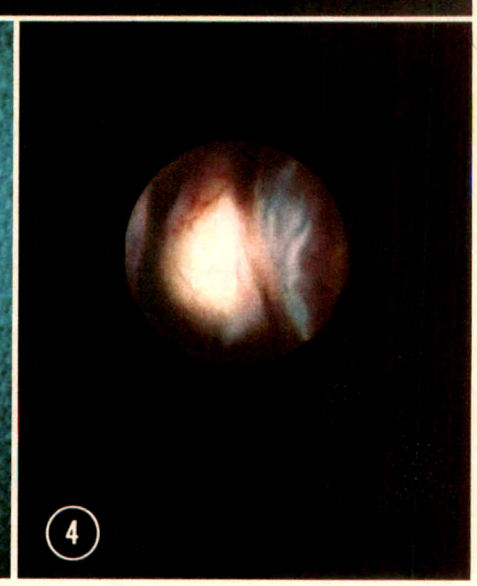
The second advantage of hysteroscopy has been illustrated by the cases presented, that is, the possibility of excision of the submucus fibroid by the transcervical route, with hysteroscopic control. Although the experience to date consists of only five cases and, therefore, is preliminary, there is no doubt that excision is feasible in selected cases, saving the patient pain and expenditure in hospital costs, as well as time lost from normal activities. Long-range beneficial effects include control of bleeding and anemia. It is too early to determine if there will be any improvement in problems of infertility and/or abortion.

Several technical points are worthy of comment. The resection has certain features in common with transurethral prostatectomy in that the larger tumors must be morcellated partially or totally for removal. As illustrated in our first case, the problems are not only to resect the tumor but also to remove it through the cervix. Instruments are being designed to accomplish this type of manipulation more easily. As the space in the endometrial cavity around the fibroid is usually









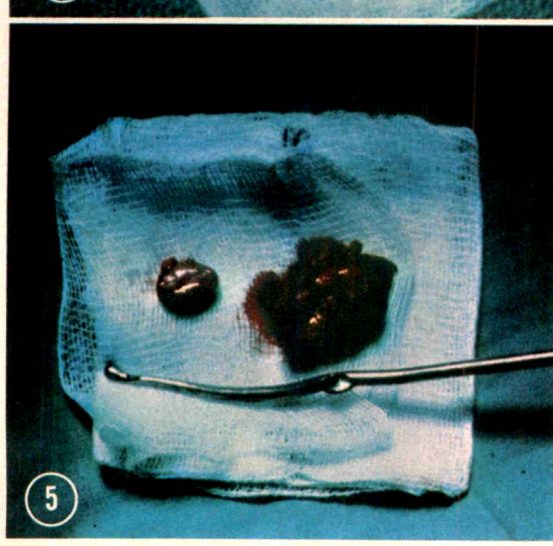


Fig. 1. View of submucus fibroid from endocervix (Case 3).
Fig. 2. View of pedicle of submucus fibroid (Case 3).
Fig. 3. Submucus fibroid following removal (Case 3).
Fig. 4. View of both submucus myomas from the cervix (Case 5).
Fig. 5. Submucus myomas following removal (Case 5).

small, the surgical excision may be tedious. The surgeon not only should be highly skilled in endoscopy and electrosurgery but also should have had considerable experience with hysteroscopy before attempting resection. We have found that resection of these tumors is feasible if the hysteroscope is employed very flexibly. If the tumor is small, the hysteroscope should be removed, and the tumor can be grasped with an ovum forceps and twisted off. Following removal, the hysteroscope is reinserted to evaluate the site for completeness of removal and to control bleeding with cautery, if necessary.

For large tumors, resection with a cutting loop or a rectoscope is feasible. Alternatively, a slender scissors or biopsy instrument may be inserted alongside the hysteroscope to manipulate the tumor mechanically with visual control. Such manipulation is only possible with high-viscosity liquids, such as 32 per cent dextran 70, because distending fluid losses through the cervix are great. In addition, bleeding during manipulation may become brisk and is more easily controlled by intermittent cauterization in the high-viscosity medium.

As for selection of the type of tumor to be resected, we have thus far limited ourselves to the pedunculated variety with a distinct stalk. The sessile type which may be partially embedded in the myometrium may also be amenable to this approach, but the risk of bleeding will probably be higher. Electrocautery in such cases will have to be carried out carefully and under laparoscopic control to ensure that the intestines are separated from the uterus. For the present, such tumors have not been approached.

In summary, this experience has demonstrated that hysteroscopy can be used to select certain submucus fibroids and perform transcervical resection effectively and safely. The follow-up to date has been satisfactory in that there was no recurrence of the abnormal vaginal bleeding with concomitant correction of the associated anemia. The effect of this approach on subsequent reproductive performance remains to be learned. The reduction in time lost from work and the avoidance of the pain and complications of laparotomy are the major advantages of this approach. However, the method requires specialized skills and equipment, is tedious, and carries potential hazards of serious bleeding and visceral burns from cautery; therefore, it should be approached with caution. These risks must also be explained to the patient, and the procedures must be carried out in the operating room with general anesthesia so that emergency laparotomy can be performed if necessary.

REFERENCES

1. McCall, M., and Bolton, K.: Martius' Gynecological Operations, Boston, 1956, Little, Brown & Company.
2. Norment, W. B., Sikes, C. H., Berry, F. X., and Bird, I.: Surg. Clin. North Am., p. 1377, 1957.
3. Neuwirth, R. S.: Hysteroscopy, Philadelphia, 1975, W. B. Saunders Company.

Antibodies to adeno-associated satellite virus and herpes simplex in sera from cancer patients and normal adults

HEATHER D. MAYOR
STEPHANIE DRAKE
JOYCE STAHMANN
DAVID M. MUMFORD
Houston, Texas

The ecologic aspects of the distribution of adeno-associated satellite virus (ASV) in the human population are of great interest because of its unconditional defectiveness and dependence on adenovirus for full and herpesvirus for partial complementation. Adenoviruses and herpesviruses are extremely common and persistent infections in man. We have developed immunofluorescent procedures for detecting the presence of satellite virus antibodies in human sera. The percentage of sera with antibodies to the ASV 2-3 complex was significantly higher in the normal group than in the cancer patients whereas there were no significant differences in herpes antibodies between the groups. The low incidence of satellite antibodies was particularly striking in patients with genital malignancies. The role of ASV's in human disease is not known. Their role in possible abrogation of oncogenesis mediated through adenoviruses or herpesviruses is worthy of further investigation.

ADENO-ASSOCIATED satellite viruses (ASV's) belong to the group of small deoxyribonucleic acid (DNA)–containing animal viruses named parvo or pico-DNA viruses. ASV's were first found in electron micrographs of crude preparations of simian and human adenoviruses.[2, 22] The original hypothesis[24] that all these viruses would be found to contain single-stranded DNA[18, 23] now has been shown to be correct. However, satellites are unique among parvo (pico-DNA) viruses in that they are unconditionally defective and need competent adenoviruses to complete their replicative cycles.[27] In addition, in the presence of herpesvirus, ASV's can partially complete their replication cycle. In this system, new satellite structural proteins can be detected and viral DNA is replicated.[7] However, complete virus particles are not formed.

Although a number of studies have shown that satellite viruses can infect human beings,[5, 6] there is no evidence that these infections result in any clinical disease.[5, 16]

The ecologic aspects of satellite virus distribution in the human population are of great interest because of their unconditional defectiveness and their dependence on adenovirus for full and herpesviruses for partial replication. Adenoviruses and herpesviruses are common and persistent infections of man. Although satellite viruses have been cultivated from isolates of human adenovirus which have been passaged only in human cells, many human adenovirus isolates have been found to be completely negative for satellites.[5, 7]

It is not clear currently whether strains of types 2 and 3 are sufficiently distinct immunologically to allow a specific serotype designation. They appear rather to represent an antigenic spectrum which more accurately could be defined as a type 2-3 complex. Studies of Parks and associates[26] on blood from the adult and pediatric population revealed serological evidence of satellite infection in almost 80 per cent of human subjects in some age groups. Antibody titers against

From the Departments of Microbiology and Immunology and Obstetrics and Gynecology, Baylor College of Medicine.

Supported by Grant DRG 1187 from the Damon Runyon–Walter Winchell Cancer Fund, New York, New York, Grant CA 14618 from the National Cancer Institute, National Institutes of Health, and the Meredity Mosle Laboratory for Cancer Research.

Received for publication December 30, 1975.

Accepted Februrary 3, 1976.

Reprint requests: Dr. Heather D. Mayor, Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030.

type 1 and type 2-3 complexes reached peak levels at two to three years of age. Type 4 antibodies were rarely noted in human blood although they are commonly found in sera from green and rhesus monkeys.[21] It is considered that their presence in human sera may result from contamination in monkey-grown viral vaccines. In children, the age-specific occurrence of neutralizing antibody increased most rapidly between four and 11 months and continued a generally steady increase to peak at eight to 14 years when almost 80 per cent of those tested had positive results.[26] This satellite serologic pattern was quite similar to the sequential incidence of antibodies to Epstein-Barr virus (EBV) and other herpesviruses and polioviruses in the Houston community.

In the presence of replicating helper adenoviruses, satellite viruses replicate infectious progeny. However, during the process, satellite viruses interfere with the replication of their helper adenoviruses and in the case of oncogenic adenoviruses appear to reduce the tumorigenicity of the adenoviruses.[13, 14, 19]

In a more recent investigation,[30] the development of tumors in newborn hamsters inoculated with highly oncogenic human adenovirus type 31 was studied. By six months of age, approximately 50 per cent of the animals inoculated with adenovirus had developed typical adenovirus tumors while in control animals which were inoculated first with ASV and then challenged 24 hours later with adenovirus less than two per cent of the animals developed tumors.

Seroepidemiologic studies by Sprecher-Goldberger and colleagues[29] have shown that the incidence of antibodies to types 1 and 3 satellite viruses measurable in the blood of a group of hospital patients is significantly lower in sera from cancer patients than in those with other nononcogenic diseases. In a more recent report,[30] these investigators found that patients with cervical cancer differed significantly from matched control subjects by a high prevalence of adenovirus antibodies in the serum in the absence of ASV type 3 antibodies. No significant correlation with the presence of herpesvirus antibodies was found. In addition, in both of these studies, based on complement-fixation (CF) procedures, only 34 per cent of control individuals were found to be positive for satellite type 3 virus antibodies.

Seroepidemiologic studies have suggested that a relationship exists between herpes simplex virus type 2 and human cervical carcinoma.[3, 25, 28] Biochemical evidence has been presented that herpesvirus infection can be found in cervical tumor cells either as antigens[4] or as DNA sequences possibly integrated into the tumor cell chromosome.[12] Duff and Rapp[10] have been able to transform hamster embryo fibroblasts with ultraviolet-irradiated herpes simplex type 2. These transformed cells were able to transcribe virus-specific ribonucleic acid (RNA) sequences common to herpesvirus types 1 and 2. These results suggested that herpesvirus type 1 might contain base sequences which are probably oncogenic.

This report sets out to determine whether a correlation exists between the presence of human cancer and the absence of antibodies to the ASV 2-3 complex as measured by a sensitive immunofluorescence procedure. In addition, demonstration of absence of satellite antibodies in herpes-positive sera of patients with genital cancer would be a potentially important finding.

Material and methods

Study groups. Sera obtained recently, stored at −70° C. from multiple ongoing studies, were thawed for these determinations. The original blood samples had been obtained from patients with various types of cancer including melanoma, leukemia, lymphoma, cervical carcinoma, and prostatic cancer. Many sera, including those from patients with infectious mononucleosis, were provided through the kindness of individual physicians who knew of our interest in this problem. Normal sera and sera from patients with a known history of herpes infections were obtained from medical students, house staff, college students, office personnel, men prior to vasectomy, and women prior to tubal ligation. Control subjects, when noted in the tables, were matched for age, sex, and socioeconomic status.

Fluorescent antibody assay and CF tests. We have developed a sensitive immunoassay system based on fluorescent antibody techniques to determine whether selected human sera drawn from adult cancer patients and the normal adult population, matched for age, sex, and race, have antibodies to the type 2-3 ASV complex.

Cover-slip cultures of green monkey kidney (BSC-1) cells were grown in Petri dishes in minimum essential medium (MEM) containing 10 per cent fetal calf serum. These cells were infected in the stationary phase with either type 2 or type 3 satellite virus and simian adenovirus SV15 as a helper. Incubation was continued in MEM containing 2 per cent fetal calf serum at 37° C. in a carbon dioxide incubator. When beginning cytopathic effects demonstrated that virus replication had occurred (usually 48 hours after incubation), cultures were harvested, dried, fixed in acetone, and stored under desiccation. These cover slips formed the stockpile for subsequent immunochemical tests with human serum samples. By using simian cells and a simian helper adenovirus, we were able to lower

Table I. Presence of antibodies to satellite virus and herpes simplex in sera

Origin of serum	Satellite 2-3 complex antibody		Herpes simplex antibody	
	No. tested	*% Positive*	*No. tested*	*% Positive*
Cancer patients	120	30*	120	70†
Normal adults (matched controls)	128	75*	128	60†

*$p < 0.001$.
†$0.20 > p > 0.10$.

Table II. Presence of antibodies to satellite virus and herpes simplex in sera

Origin of serum	Satellite 2-3 complex antibody		Herpes simplex antibody	
	No. tested	*% Positive*	*No. tested*	*% Positive*
Genital cancer patients	70	14*	70	91†
Normal adults with recurrent herpes infections	33	85*	33	79†

*$p < 0.001$.
†$0.10 > p > 0.05$.

Table III. Presence of antibodies to satellite virus and herpesvirus in mononucleosis sera*

Origin of serum	Satellite 2-3 complex antibody		Herpes simplex antibody	
	No. tested	*% Positive*	*No. tested*	*% Positive*
Adult mononucleosis patients	24	86	24	50

*All these sera were positive for EBV.

the level of nonspecific staining in the system to a negligible level. Coded serum samples from the human population were heat inactivated at 56° C. for 30 minutes, diluted 1/10 in phosphate-buffered saline, and reacted with the satellite-infected cover slips by the indirect fluorescent antibody procedure with the use of fluorescein-labeled anti-human immunoglobulin G (IgG) obtained from rabbits at a 1/10 dilution. Samples from each batch of infected cover slips were first confirmed to be positive by their reactions with standard serum known to contain anti–type 2-3 complex antibodies. Negative controls included the patient's serum followed by anti-IgG conjugate with uninfected BSC-1 cells and BSC-1 cells infected with SV15 alone and the anti-IgG conjugate alone reacted with BSC-1 cells infected with SV15 and ASV. Cover slips infected with either type 2 or type 3 performed equally well in these tests, confirming the strength of the cross-reactions.

The stained cover slips were examined in blind study and scored as positive or negative for antibodies to the type 2-3 satellite virus complex. Only cover slips demonstrating brilliant, clear nuclear fluorescence typical of ASV antigen in at least 10 per cent of the cells were scored as positive. Antibodies against herpes simplex viruses were determined by CF procedures standard at the Houston City Health Department (Director, Dr. Reuben Wende, now at Baylor College of Medicine, through whose kindness these tests were performed). Sera were recorded as positive when CF was complete at a dilution of 1:4 or greater. Herpes simplex antigen was supplied by Flow Labs, Inc.* The test does not discriminate between antibodies to herpesvirus type 1 and type 2, but, due to the marked relatedness between the two strains and the possible oncogenic potential of all herpesvirus, this limitation was not considered a disadvantage.

Results

Table I shows the distribution of antibodies to the satellite type 2-3 complex and to herpes simplex in adult cancer patients with a variety of neoplastic diseases and in matched control subjects. The percentage of ASV 2-3 complex antibodies was significantly higher in the normal sera than in sera from the cancer patients ($p < 0.001$). There were no significant differences in herpes antibodies between the two groups ($0.20 > p > 0.10$). Table II shows the distribution of antibody to the satellite type 2-3 complex and to herpes simplex in otherwise normal adults who reported or were actually suffering from recurrent herpes simplex infections and patients with genital malignancies. Again the percentage of ASV 2-3 complex antibodies was significantly higher in the normal group than in the tumor group. However, both groups demonstrated a high percentage of herpesvirus antibodies; in fact, 90 per cent of the genital cancer patients tested demonstrated herpes antibodies. Sera from mononucleosis patients demonstrated a high proportion of antibodies to the satellite type 2-3 complex (Table III).

Comment

By an immunofluorescent assay, this study has revealed clear evidence of a low prevalence of antibodies

*12601 Twinbrook Pkwy., Rockville, Maryland 20852.

to the satellite 2-3 complex in cancer patients as compared with matched control subjects. The lowered incidence is particularly marked in the cervical cancer group (14 per cent). These results are striking when compared to the incidence of ASV-positive results (80 per cent) in our matched control group which is quite in line with previous reports of the ASV incidence in mammals. Possible "positive" control groups (dermatologic herpes simplex patients and infectious mononucleosis patients), when monitored for ASV incidence, reinforce the variance found in the cancer group. This difference is probably not due to a general immunodepressive condition as cancer patients did not suffer from control subjects in their ability to produce herpes simplex antibodies and in other immune assays performed on both groups but not reported here. Although this study must be considered essentially a pilot one (the groups of genital cancer patients and normal adults with recurrent herpes infections are admittedly small), nonetheless, the presence of such low levels of antibodies to the ASV 2-3 complex in patients with genital cancer who also have "normal" incidence titers or herpes simplex virus antibody is striking.

The possibly slightly lowered incidence of herpes simplex titers (50 per cent) found in the mononucleosis patient group when compared to the control group (Table III) is probably not significant but may partially reflect the younger age group of the mononucleosis sample (15 to 35 years old). The incidence of positivity for herpes simplex antibodies rises with age as with many other natural viral exposures. In one reported control series, the incidence of HSV antibody in the group 15 to 34 years old was 50 per cent versus 84 per cent for the group 35 to 75 years old.[15] The former rate is obviously in keeping with the incidence of positivity found in our mononucleosis patients who are predominantly in the same age bracket. The assay procedures, immunofluorescence for satellite virus titers and CF for herpes titers, are not necessarily equal in sensitivity and they do not allow us to comment on possible variations in immunoglobulin class expression which might occur in cancer patients when compared to the control population. Subsequent investigations may be directed to these factors.

Although satellite viruses have been shown to reduce the tumorigenicity of adenoviruses in animal systems,[20] it has not been possible to test whether they also play a role in control or prevention of potential oncogenesis of herpesviruses due to the virulence in newborn hamsters of the herpes agents. From the rationale that the ultraviolet irradiation of known human viruses reduces their infectivity more rapidly than their oncogenicity,[8, 9] Duff and Rapp[10] were able to transform hamster cells in vitro with ultraviolet-irradiated herpesvirus type 2 and more recently with type 1.[11] It may be timely to attempt to abrogate this kind of malignant transformation with prior inoculation with ASV.

An association between cancer of the uterine cervix and herpesvirus type 2 which is venereally transmitted has been demonstrated.[1] Herpesvirus types 1 and 2 have been shown to have oncogenic potential in in vitro systems, and evidence for the presence of herpesvirus group genetic information in neoplastic cells and tissues is accumulating. The role of ASV's in human disease is not known, although the dependence of satellite viruses on adenoviruses and herpesviruses, two common infections of man, for their genetic expression is well documented. The possibility that the satellite agent may have "housekeeping" properties involved in overt expression of potential oncogenic viral DNA sequences in preference to their integration into susceptible host cells in a cryptic form is provocative and worthy of further investigation.

REFERENCES

1. Adam, E., Rawls, W. E., and Melnick, J. L.: The association of herpes virus type 2 infection and cervical cancer, Prev. Med. **3:** 122, 1974.
2. Atchison, R. W., Casto, B. C., and Hammon, W. McD.: Adenovirus-associated defective virus particles, Science **149:** 754, 1965.
3. Aurelian, L.: Possible role of herpes virus hominis, type 2, in human cervical cells, Fed. Proc. **31:** 1651, 1972.
4. Aurelian, L., Royston, I., and Davis, H. J.: Antibody to genital herpes simplex virus association with cervical atypia and carcinoma *in vitro*, J. Natl. Cancer Inst. **45:** 455, 1970.
5. Blacklow, N. R., Hoggan, M. D., Kapikian, A. Z., Austen, J. B., and Rowe, W. P.: Epidemiology of adenovirus-associated virus infection in a nursery population, Am. J. Epidemiol. **88:** 368, 1968.
6. Blacklow, N. R., Hoggan, M. D., and Rowe, W. P.: Isolation of adenovirus associated viruses from man, Proc. Natl. Acad. Sci. U. S. A. **58:** 1410, 1967.
7. Boucher, D. W., Melnick, J. L., and Mayor, H. D.: Nonencapsidated infectious DNA of adeno-satellite virus in cells coinfected with herpesvirus, Science **173:** 1243, 1971.
8. Defendi, V., and Jensen, F.: Oncogenicity of DNA tumor viruses: enhancement after ultraviolet and cobalt-60 radiation, Science **157:** 703, 1967.
9. Duff, R., Knight, P., and Rapp, F.: Variation in oncogenic and transforming potential of PARA (defective SV40)–adenovirus 7, Virology **47:** 849, 1972.
10. Duff, R., and Rapp, F., Properties of hamster embryo fibroblasts transformed *in vitro* after exposure to ultraviolet and irradiated herpes simplex virus type 2, Virology **8:** 469, 1971.
11. Duff, R., and Rapp, F., The oncogenic transformation of

hamster embryo cells after exposure to inactivated herpes simplex virus, type 1, J. Virol. **12:** 209, 1973.
12. Frenkel, N., Roizman, B., Cassai, E., and Nahmias, A.: A DNA fragment of herpes simplex 2 and its transcription in tumor cervical cancer tissue, Proc. Natl. Acad. Sci. U. S. A. **69:** 3784, 1972.
13. Gilden, R. V., Kern, J., Beddow, T. G., and Huebner, R. J.: Oncogenicity of mixtures of adeno-associated virus and adenovirus type 12, Nature **219:** 80, 1968.
14. Gilden, R. V., Kern, J., Beddow, T. G., and Huebner, R. J.: Oncogenicity of mixtures of adeno-associated virus and adenovirus type 12, Nature **220:** 1139, 1968.
15. Goldman, J. M., and Aisenberg, A. C.: Incidence of antibody to EB virus, herpes simplex, cytomegalovirus and Hodgkin's disease, Cancer **70:** 327, 1970.
16. Hoggan, M. D.: Small DNA viruses, *in* Maramorosch, K., and Kurstak, E., editors: Comparative Virology, New York, 1971, vol. 1, Academic Press, Inc., pp. 43-79.
17. Hoggan, M. D., Blacklow, N. R., and Rowe, W. P.: Study of small DNA viruses found in various adenovirus preparations: physical, biological, and immunological characteristics, Proc. Natl. Acad. Sci. U. S. A. **55:** 1467, 1966.
18. Jamison, R. M., and Mayor, H. D.: Acridine orange staining of purified rat virus strain X14, J. Bacteriol. **90:** 1486, 1965.
19. Kirschstein, R. L., Smith, K. O., and Peters, E. H.: Inhibition of adenovirus 12 oncogenicity by adeno-associated virus, Proc. Soc. Exp. Biol. Med. **128:** 670, 1968.
20. Mayor, H. D., Houlditch, G. S., and Mumford, D. M.: Influence of adeno-associated satellite virus in adenovirus-induced tumors in hamsters, Nature (New Biol.) **241:** 44, 1973.
21. Mayor, H. D., and Ito, M.: Distribution of antibodies to type 4 adeno-associated satellite viruses in simian and human sera, Proc. Soc. Exp. Biol. Med. **126:** 723, 1967.
22. Mayor, H. D., Jamison, R. M., Jordan, L. E., and Melnick, J. L.: Structure and composition of a small particle prepared from a simian adenovirus, J. Bacteriol. **90:** 235, 1965.
23. Mayor, H. D., Jordan, L., and Ito, M.: Deoxyribonucleic acid of adeno-associated satellite virus, J. Virol. **4:** 191, 1969.
24. Mayor, H. D., and Melnick, J. L.: Small deoxyribonucleic acid-containing viruses (picodnavirus group), Nature **210:** 331, 1966.
25. Naib, Z. M., Nahmias, A. J., Josey, W. E., and Kramer, J. H.: Genital herpetic infection: associated with cervical dysplasia and carcinoma, Cancer **23:** 940, 1969.
26. Parks, W. P., Boucher, D. W., Melnick, J. L., Taber, L. H., and Yow, M. D.: Seroepidemiological and ecological studies of the adenovirus-associated satellite viruses, Infect. Immun. **2:** 716, 1970.
27. Parks, W. P., Melnick, J. L., Rongey, R., and Mayor, H. D., Physical assay and growth cycle structure of a defective adeno-satellite virus, J. Virol. **1:** 171, 1967.
28. Rawls, W. E., Tomplins, W. A. F., and Melnick, J. L.: Association of herpesvirus type 2 and carcinoma of the uterine cervix, Am. J. Epidemiol. **89:** 547, 1969.
29. Sprecher-Goldberger, S., Dekegal, D., Otten, J., and Thiry, L.: Incidence of antibodies to adenovirus-associated viruses in patients with tumors or other diseases, Arch. Virusforsch. **30:** 16, 1970.
30. Sprecher-Goldberger, S., Thiry, L., Lefebvre, W., Dekegal, D., and de Halleux, F.: Complement-fixation antibodies to adenovirus-associated viruses. Adenoviruses, cytomegaloviruses and herpes simplex viruses in potential with tumors and in control individuals, Am. J. Epidemiol. **94:** 331, 1971.

Obstetrics and Gynecology Review Course

The "Obstetrics and Gynecology Review Course" will be held October 2-10, 1976, at the Royal Biscayne Beach Hotel and Racquet Club, Key Biscayne, Florida. It is designed for obstetricians and gynecologists who are preparing for certification examinations or who wish to be brought up to date in all aspects of obstetrics and gynecology. The course will be credited in American Medical Association Category 1 for 53 hours minimum and 69 hours maximum. The Program Director is William Little, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of Miami School of Medicine. For further information, contact: Division of Continuing Medical Education, University of Miami School of Medicine, P. O. Box 520875, Miami, Florida 33152. Telephone: (305) 547-6716.

Carcinoembryonic antigen in intraepithelial neoplasia of the uterine cervix

J. R. VAN NAGELL, JR., M.D.
W. R. MEEKER, M.D.
J. C. PARKER, JR., M.D.
RAFIAH KASHMIRI, M.S.
VIOLA McCOLLUM, B.A.
Lexington, Kentucky

Carcinoembryonic antigen (CEA) was elevated (>2.5 ng. per milliliter) in 29 of 100 patients with cervical intraepithelial neoplasia (CIN). CEA concentration was related to the amount of intraepithelial neoplasia and to the presence of glandular extension. Lymphoplasmacytic infiltration of tumor cells was unrelated to CEA levels. CEA values returned to normal within 8 weeks following surgery in 77 per cent of patients. A persistently elevated (>5.0 ng. per milliliter) plasma CEA value following conization was associated with residual CIN in the cervix. These results suggest that sequential CEA determinations may be of value in the follow-up of those cervical cancer patients who initially have high plasma antigen levels.

SINCE ITS original description by Gold and Freedman[4, 5] in 1965, carcinoembryonic antigen (CEA) has been identified in the tumors and plasma of patients with a variety of invasive cancers.[10, 13, 14, 20] In a previous investigation from this institution,[19] 80 per cent of patients with invasive squamous cell carcinoma of the cervix were found to have elevated (>2.5 ng. per milliliter) plasma CEA levels. The incidence of elevated plasma CEA was directly related to the stage of disease and to the presence of vessel invasion by tumor cells. Very little has been reported, however, concerning the presence of this antigen in patients with noninvasive cervical lesions.

The present prospective study was undertaken to determine (1) the incidence of elevated plasma CEA in patients with cervical intraepithelial neoplasia (CIN), (2) the relationship of CEA elevation to the extent and histomorphologic characteristics of cervical intraepithelial tumors, and (3) the effect of surgical removal of these tumors on plasma CEA.

From the Departments of Obstetrics and Gynecology, Surgery, and Pathology, University of Kentucky Medical Center.

Received for publication October 1, 1975.

Accepted December 12, 1975.

Reprint requests: Dr. John R. van Nagell, Jr., Department of Obstetrics and Gynecology, University of Kentucky, Lexington, Kentucky 40506.

Material and methods

Clinical material. From January, 1974, through April, 1975, 100 patients with CIN underwent cervical conization on the Gynecologic Oncology Service at the University of Kentucky Medical Center. Clinical evaluation of each patient was based upon physical, radiologic, and laboratory findings prior to surgery. Data were collected concerning age, parity, height, weight, and history of cigarette smoking for all patients. Plasma samples for CEA were drawn on the day prior to conization, 2 days following surgery, and 8 weeks thereafter. Eight to 20 sections (mean 11.0) of each conization specimen were cut in order to define the extent of intraepithelial neoplasia. Each histologic section was reviewed and classified according to the following criteria: cell type, extension of neoplasia to endocervical glands, benign adenomatoid or endocervical glandular hyperplasia (Fig. 1), dyskeratosis or abnormal keratin production (Fig. 2), and lymphoplasmacytic infiltration. In addition, cervical epithelial abnormalities were further subdivided into moderate dysplasia, severe dysplasia, or carcinoma in situ according to the morphologic criteria reported by Johnson and colleagues.[8] A group of 176 healthy volunteers and 95 patients with benign gynecologic disease studied previously at this institution by van Nagell and associates[19] served as control populations for this investigation.

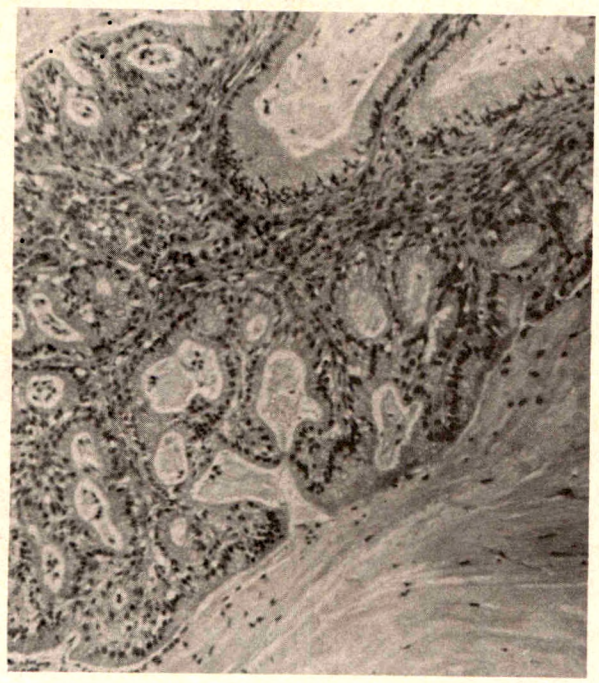


Fig. 1. Benign glandular (adenomatoid) hyperplasia characterized by prominent small mucus-producing, back-to-back endocervical glands with scattered mononuclear inflammatory cells. (Hematoxylin and eosin; ×100.)

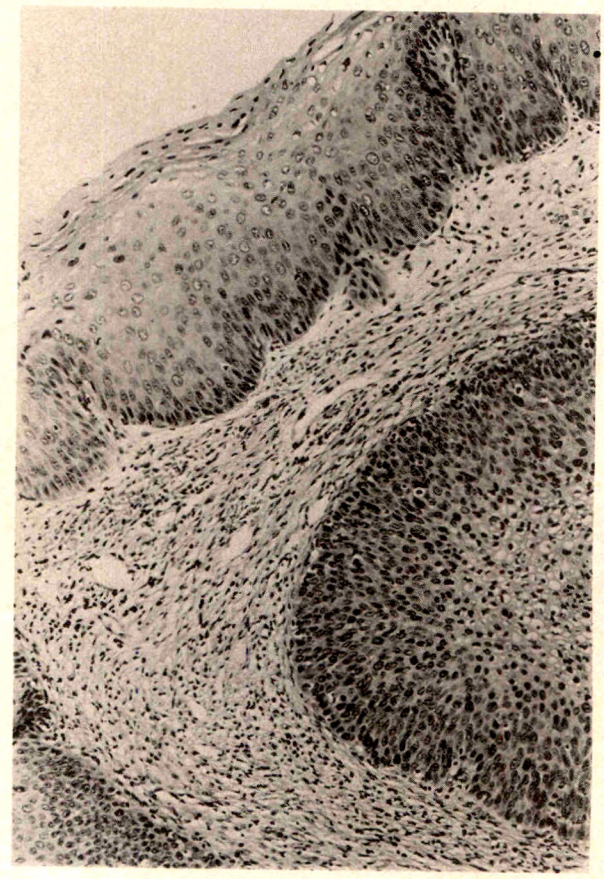


Fig. 2. Dyskeratosis—keratin-production by a normally non-keratizing stratified squamous epithelium. (Hematoxylin and eosin; ×100.)

Methods

Plasma CEA levels were determined as previously described by LoGerfo and associates[10] and Meeker and associates.[11] Briefly, 7 ml. of blood were drawn into tubes containing sodium edetate (Na-EDTA) and the plasma was withdrawn following centrifugation. Then 1 ml. aliquots of plasma were extracted with 0.6M perchloric acid and the samples were analyzed immediately by radioimmunoassay for CEA by the Hansen Z-gel procedure. Using this method, Chu and Reynoso[1] were able to distinguish reliably between plasma levels of 0 and 0.5 ng. per milliliter. CEA reagents were kindly provided by Hoffmann-La Roche Laboratories, Nutley, New Jersey. A plasma CEA value of 2.5 ng. per milliliter was taken as the upper limit of normal.

Results

Plasma CEA values in the patients studied are presented in Table I. Absolute plasma levels of CEA varied from 0 to 25 ng. per milliliter (mean 1.7 ng. per milliliter). Twenty-nine per cent of patients with CIN had elevated (>2.5 ng. per milliliter) levels of plasma CEA. This was significantly ($p < 0.002$) higher than that in normal healthy volunteers. Of those patients with abnormally elevated CEA titers, nine (27.6 per cent) had values above 5.0 ng. per milliliter and one patient had a plasma CEA value greater than 10.0 ng. per milliliter. Patients with CIN had higher plasma CEA values than those with benign gynecologic disease, but this difference was not significant ($p < 0.16$) in the numbers of patients studied.

The clinical characteristics of patients with elevated plasma CEA values did not differ from those with normal CEA values (Table II). This included the presence of cigarette smoking which was essentially the same in both groups. Histomorphologic findings in conization specimens are illustrated in Table III. Abnormally elevated plasma CEA levels were significantly ($p < 0.001$) correlated with the extent of CIN as manifested by the number of sections involved and the extension of tumor into the endocervical glands. Likewise, the production of keratin by cervical epithelium was associated with elevated plasma CEA titers. Both lymphoplasmacytic infiltration and benign adenomatoid hyperplasia of the endocervical glands were unrelated to the level of CEA. The incidence of abnormally elevated CEA increased with the progres-

Table I. Carcinoembryonic antigen values in patients studied

	No. of patients	CEA values (ng./ml.)			
		<2.5	2.5-4.9	5.0-10.0	>10
Healthy volunteers	176	157 (89%)	17 (10%)	2 (1%)	0 (0%)
Benign gynecologic disease	95	78 (82%)	13 (14%)	4 (4%)	0 (0%)
Cervical intraepithelial neoplasia	100	71 (71%)	20 (20%)	8 (8%)	1 (1%)

Table II. Clinical characteristics of patients related to plasma carcinoembryonic antigen values

	Plasma CEA levels	
	<2.5 ng./ml.	>2.5 ng./ml.
Patients	71	29
Age (yr.)	32	35
Height (in.)	62.5	63
Weight (lb.)	145	143
Parity	3.4	3.8
Smoking (packs per day)	0.8	0.8

sion of the histologic epithelial abnormalities from moderate dysplasia to carcinoma in situ (Table IV).

Follow-up

Twenty-six of the 29 patients with abnormal plasma CEA levels returned for repeat CEA determinations 2 days and 8 weeks following conization. Plasma CEA titers returned to normal by the second postoperative day in 23 per cent of the patients and by the eighth week following surgery in 77 per cent of the patients. Hysterectomy was performed 8 weeks after conization in 19 patients. Six patients had residual intraepithelial carcinoma in the uterus following conization. Plasma CEA determinations 8 weeks postconization in patients with residual uterine carcinoma in situ ranged from 2.0 to 11.7 ng. per milliliter (mean 5.4 ng. per milliliter). In contrast, patients with no evidence of residual disease had plasma CEA values from 0 to 4.8 (mean 2.0 ng. per milliliter). Three patients had plasma CEA values greater than 5.0 ng. per milliliter 8 weeks following conization, and all three had residual intraepithelial carcinoma in the uterine specimen.

Comment

Intraepithelial neoplasia had been considered by many investigators to be an intermediate step in the biologic progression toward invasive malignancy, particularly in the uterine cervix. Neoplastic change in cervical epithelium has been recognized colposcopically, histologically, and even genetically.[8, 15–18] Richart and Wilbanks[15] and Granberg,[6] for example, noted an increase in abnormal chromosome numbers in cervical epithelium cells progressing from in situ to invasive cervical carcinoma. Very little has been reported, however, concerning the expression of antigenic determinants in intraepithelial cancer.

Carcinoembryonic antigen was originally thought to be a tumor antigen specifically associated with adenocarcinoma of the colon.[4, 5] However, it has more recently been identified in the plasma of normal individuals.[2] The difference in CEA levels between benign and malignant tissues appears, therefore, to be quantitative rather than qualitative. In addition, LoGerfo and colleagues[10] have demonstrated an antigenic site on CEA common to both entodermally and nonentodermally derived tissues. This has been substantiated by the identification of CEA in the tumors and plasma of patients with invasive cervical and ovarian cancer which has physicochemical and immunologic properties similar to colonic cancer CEA.[12, 20, 21]

The findings of the present study demonstrate the lack of specificity of CEA as a diagnostic method in patients with CIN. Only 29 per cent of these patients had elevated plasma CEA values. This was significantly higher than that in normal control patients, but lower than that in patients with invasive gynecologic malignancy.

The correlation of plasma CEA to the extent of cervical intraepithelial disease is consistent with similar findings in patients with invasive cervical cancer.[3, 19] Elevation of plasma CEA seems related to the amount of tumor present whether the tumor is intraepithelial or has invaded the cervical stroma.

Histomorphologic criteria of the cervix were of limited value in predicting CEA elevation. The association of increased plasma CEA levels with the production of keratin by the cervical epithelium (dyskeratosis) may simply indicate a positive relationship between CEA expression and chronic cervical inflammation. Plasma CEA has previously been reported to be increased in certain inflammatory diseases of the bowel and pelvis.[5, 11, 15] The lack of correlation between lymphoplasmacytic infiltration and CEA elevation is not surprising since this nonspecific finding was present in 78 per cent of all sections reviewed.

Analysis of follow-up data indicate that complete

Table III. Histomorphologic characteristics of cone specimens

	Plasma CEA levels		
	<2.5 ng./ml.	*>2.5 ng./ml.*	*Significance*
Sections involved with CIN	332/791 (40.7%)	211/338 (62.4%)	$p < 0.001$
Glandular involvement with CIN	25/71 (35.2%)	21/29 (72.4%)	$p < 0.001$
L-P infiltrate	53/71 (74.6%)	25/29 (86.2%)	NS*
Adenomatoid hyperplasia	5/71 (7.0%)	3/29 (10.7%)	NS
Dyskeratosis	18/71 (25.4%)	17/29 (58.6%)	$p < 0.01$

*NS = Nonsignificant.

Table IV. Carcinoembryonic antigen values related to the severity of cervical intraepithelial neoplasia

	Plasma CEA levels		
	No. of patients	*<2.5 ng./ml.*	*>2.5 ng./ml.*
Moderate dysplasia	26	20 (76.9%)	6 (23.1%)
Severe dysplasia	19	14 (73.7%)	5 (26.3%)
Carcinoma in situ	55	37 (67.3%)	18 (32.7%)
Total	100	71 (71%)	29 (20%)

excision of intraepithelial cancer was associated with a return to normal plasma CEA titers within 8 weeks in over three fourths of the cases. This is similar to previous findings in patients with cervical, ovarian, and colonic carcinomas.[7, 9, 19, 22]

The use of CEA as an aid in determining residual in situ carcinoma in the cervix following cervical conization is potentially important. Conization is curative in approximately 80 per cent of patients with intraepithelial cervical carcinoma, but it is often difficult to predict residual cervical or uterine disease by examination of the conization specimen. Although a persistently elevated plasma CEA (>5.0 ng. per milliliter) following conization was uniformly associated with residual in situ carcinoma in the cervix, the numbers of patients with this finding was small. Consequently, this observation will have to be evaluated in larger numbers of patients.

Further studies concerning tissue localization and metabolism of CEA in patients with gynecologic malignancies are needed. However, these results and those of other investigations[7, 16] suggest that sequential CEA determinations may be of value in the follow-up of those cervical cancer patients who have high initial plasma or tumor levels of antigen.

The authors would like to express their thanks to Dr. Hans Hansen and Hoffmann-La Roche, Inc., for supplying reagents for the radioimmunoassay, and to John Haley, Ph.D., of the Department of Behavioral Science, University of Kentucky Medical Center, for statistical evaluation of the data.

REFERENCES

1. Chu, T. M., and Reynoso, G.: Evaluation of a new radioimmunoassay method for carcinoembryonic antigen in plasma with the use of Zirconyl phosphate gel, Clin. Chem. **18:** 918, 1972.
2. Chu, T. M., and Reynoso, G.: Demonstration of carcinoembryonic antigen in normal human plasma, Nature **238:** 152, 1972.
3. DiSaia, P. J., Haverback, B. J., Dyce, B. J., and Morrow, C. P.: Carcinoembryonic antigen in patients with gynecologic malignancies, Am. J. Obstet. Gynecol. **121:** 159, 1975.
4. Gold, P., and Freedman, S. O.: Demonstration of tumor specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques, J. Exp. Med. **121:** 439, 1965.
5. Gold, P., and Freedman, S. O.: Specific carcinoembryonic antigens of the human digestive system, J. Exp. Med. **121:** 467, 1965.
6. Granberg, I.: Chromosomes in preinvasive, microinvasive and invasive cervical carcinoma, Hereditas **68:** 165, 1971.
7. Holyoke, D., Reynoso, G., and Chu, T. M.: Carcinoembryonic antigen in patients with carcinoma of the digestive tract, Ann. Surg. **176:** 559, 1972.
8. Johnson, L. D., Easterday, C. L., Gore, H., and Hertig, A. T.: The histogenesis of carcinoma in situ of the uterine cervix, Cancer **17:** 213, 1964.
9. Khoo, S. K., and MacKay, E. V.: Carcinoembryonic antigen in cancer of the female reproductive system—sequential levels and effects of treatment. Aust. N. Z. J. Obstet. Gynecol. **13:** 1, 1973.
10. LoGerfo, P., Krupey, J., and Hansen, H. J.: Demonstration of an antigen common to several varieties of neoplasia—assay using Zirconyl phosphate gel, N. Engl. J. Med. **285:** 138, 1971.
11. Meeker, W. R., Kashmiri, R., Hunter, L., Clapp, W., and Griffen, W. O.: Clinical evaluation of carcinoembryonic antigen test, Arch. Surg. **107:** 266, 1973.
12. Pletsch, Q. A., van Nagell, J. R., Jr., and Goldenberg, D. M.: Characterization of carcinoembryonic antigen in the plasma and tumors of patients with ovarian cancer, Proc. Am. Assoc. Cancer Res. **15:** 146, 1974.
13. Reynoso, G., Chu, T. M., Guinan, P., and Murphy, G. P.: Carcinoembryonic antigen in patients with tumors of the urogenital tract, Cancer **30:** 1, 1972.

14. Reynoso, G., Chu, T. M., Holyoke, D., Cohen, E., Nemoto, T., Wang, J. J., Chuang, J., Guinan, P., and Murphy, G. P.: Carcinoembryonic antigen in patients with different cancers, J. A. M. A. **220:** 361, 1972.
15. Richart, R., and Wilbanks, G.: The chromosomes of human intraepithelial neoplasia: Report of cases of cervical intraepithelial neoplasia and review, Cancer Res. **26:** 60, 1966.
16. Stafl, A., and Mattingly, R. F.: Colposcopic diagnosis of cervical neoplasia, Obstet. Gynecol. **41:** 168, 1973.
17. Stanley, M. A., and Kirkland, J. A.: Chromosome and histologic patterns of preinvasive lesions of the cervix, Acta Cytol. **19:** 142, 1975.
18. Townsend, D. E., Ostergard, D. R., Mishell, D. R., and Hirose, F. M.: Abnormal papanicolaou smears—evaluation by colposcopy, biopsies and endocervical curettage, Am. J. Obstet. Gynecol. **108:** 429, 1970.
19. van Nagell, J. R., Jr., Meeker, W. R., Parker, J. C., Jr., and Harralson, J. D.: Carcinoembryonic antigen in patients with gynecologic malignancy, Cancer **35:** 1372, 1975.
20. van Nagell, J. R., Jr., Pletsch, Q. A., and Goldenberg, D. M.: A study of cyst fluid and plasma carcinoembryonic antigen in patients with cystic ovarian neoplasms, Cancer Res. **35:** 1433, 1975.
21. van Nagell, J. R., Jr., Pletsch, Q. A., and Goldenberg, D. M.: Carcinoembryonic antigen in squamous cell carcinoma of the cervix, Gynecol. Invest. **6:** 40, 1975.
22. Zamcheck, N., Moore, T. L., Dhar, P., and Kupchik, H.: Immunologic diagnosis and prognosis of human digestive cancer-carcinoembryonic antigens, N. Engl. J. Med. **286:** 83, 1972.

A hypothesis: The role of a high-risk male in the etiology of cervical carcinoma

A correlation of epidemiology and molecular biology

ALBERT SINGER, PH.D.(SYD.), D.PHIL.(OXON), M.R.C.O.G.
Sheffield, England
BEVAN L. REID, M.D., B.V.SC.
Sydney, Australia, and Birmingham, England
MALCOLM COPPLESON, M.D., F.R.C.O.G.
Sydney, Australia

Certain impressive epidemiological evidence appearing in the last few years leads to the conclusion that some males are more prone to have a spouse with squamous cancer of the cervix than others. Advances in knowledge in other fields, especially at the molecular biological level, enable speculation on reasons for this curious conclusion. These readily testable theories, together with an outline of the evidence on which they rest, form the substance of this hypothesis.

THE PUBLICATION of no fewer than 40 papers since the report of Rigoni-Stern[1] in Verona in 1842 dealing with women and girls at special risk of developing squamous cancer of the cervix attests to the preoccupation of epidemiologists with the female. A reasonable degree of certainty now surrounds the characteristics of those women at high risk,[2, 3] especially their early age of first coitus and a cluster of epidemiological variables which are dependent on this key factor, such as early marriage, low socioeconomic class, number of coital partners, and nonmembership in a religious group.[4, 5] Evidence of this kind led us[6–8] to propose that a carcinogen is present in the male sperm and that it acts on a target cell which we regard as the stem cell of an important phase of epithelial transition on the cervix known as metaplasia. During this process columnar epithelium of the cervical canal is replaced quite physiologically by stratified squamous epithelium.

From the Department of Obstetrics and Gynaecology, University of Sheffield, and the Jessop Hospital for Women (Dr. Singer); Queen Elizabeth Research Institute for Mothers and Infants, University of Sydney, and the Department of Obstetrics and Gynaecology, University of Birmingham, Birmingham Maternity Hospital (Dr. Reid); and the Department of Obstetrics and Gynaecology, King George V Hospital (Dr. Coppleson).

Received for publication October 7, 1975.

Accepted December 16, 1975.

Reprint requests: Dr. Albert Singer, Department of Obstetrics and Gynecology, Jessop Hospital for Women, University of Sheffield, Sheffield S3 7RE, England.

The high-risk male-epidemiological evidence

Epidemiological opinion is equally firm that the disease can be properly regarded as venereal.[2, 9, 10] It is not surprising then that the possible complicity of the male as carcinogen donor has recently come under attention so that, as in the case of the female, a specific group of males is increasingly being regarded as at higher risk.[11–14] Suspicions as to the existence of such a group derives from evidence of various direct and indirect sources.

Indeed, two broad categories of epidemiological clues can be recognized in the male: (1) the association of cervical cancer with genital cancer at other sites or with venereal disease, or with the evidence of sexual promiscuity; and (2) those from traditional demographic studies correlating cervical cancer or positive cervical cytology with the occupational group of the husband.

In the first category, Martinez[15] observed a higher incidence than expected of cervical cancer in the wives of husbands with penile cancer. Feminella[16] in New York studied 101 wives of men with prostate cancer.

Three developed invasive cervical disease and two possessed an abnormal cervical smear. This incidence is higher than would normally be expected in such a population. Blythe-Smith and Jenkins[17] mapped the high frequency of premalignant and malignant lesions within a housing estate in Atlanta of indigent Negro women. They were able to indicate a cohabitation relationship between some of the affected women with specific males.

The sexual behavior of Jewish husbands has been the subject of some enquiry in the literature because their wives belong to a well-studied group of women considered to be at low risk for the development of cervical neoplasia.[4, 5] It is suggested[18, 19] that the increasingly liberal sexual behavior of the Jewish male may be responsible for the development of cervical carcinoma in many Jewish women in whom Martin[19] could find "no accepted behavioral factor of etiological significance." He also found that 80 percent of husbands of Jewish women with this neoplasm had a history of venereal disease. Pridan and Lilienfeld[20] also showed that 80 percent of Jewish males whose wives had this malignancy had more than nine sexual partners compared with 44 percent in a matched control group. The increasing frequency of venereal infections in Jewish males has been suggested by Ravich[21] to be associated with a slight but noticeable rise in their rate of prostate cancer.[22] Studies in Israel[23] have shown a difference in the rate of this cancer between occidental and oriental Jews. This community difference mirrors a similar relationship in the distribution of cervical cancer between European (Rumanian) and oriental (Yeminite) Jewish women residing in Israel.[24] It is believed that liberal sexual behavior is commoner among the former. Before leaving the topic of these Israeli figures, it is relevant to mention again the report of Lilienfeld and Pridan[20] concerning the over twofold higher incidence of widows among women with cervical cancer. This curious fact has again been observed in an Australian study,[25] where the incidence of widows was even higher. We could well ask what caused the death of the spouse in these cases.

Traditional demographic studies have evaluated more precisely an opinion widely shared by practicing gynecologists for many years emphasizing the importance of the contribution of a low socioeconomic environment to the origin of squamous cancer of the cervix.[26–28] As long ago as 1908, Theilhaber and Greischer[29] in Munich showed a sixfold increase in the risk of developing the disease among the wives of "day laborers, unskilled workers, agricultural laborers, paupers, factory hands, and lower officials" as compared with the wives of "physicians, lawyers, heads of firms, persons of independent means, and high officials." More recently in Britain, Wakefield and associates[30] on the basis of positive cytology and Beral[9] on the basis of standardized mortality rates have shown an almost linear correlation between incidence and husband's occupation based on the classification of the Registrar General. There was an over threefold difference of incidence between the wives of manual laborers compared with those of men in professional occupations (Table I).

Table I. Standardized mortality ratios for cervical carcinoma by husbands' occupations in married women.

Occupations of husbands	*Standardized Mortality Ratios*	
	Wakefield and et al.[30] *(1973)*	*Beral*[9] *(1974)*
Fishermen, seamen, deck and engine-room ratings, barge and boatmen	260	257-263
Laborers	180	222
Crane and hoist operators	150	159
Transport and long-distance lorry drivers	140	168
Lodginghouse and hotel keepers	—	150
Textile workers	150	—
Miners and quarrymen	133	—
Gas, coke, and chemical workers	120	—
Gardeners and groundsmen, service, sport, and recreation workers	115	98
Clerical workers	67	40-64
Civil engineers	—	60
Administrators, managers, and senior government officials	50	40
Teachers	—	30
Scientists	—	17
Clergymen	—	12

Derivation of the molecular hypothesis

It seems justified to speak of the existence of a group in the male population at high risk[11–14] in the same way although with less documentation, as epidemiologists have delimited a female counterpart.[2–5] A multidisciplined attack at the biological and molecular level on the latter problem has allowed a more precise definition of the tissue at risk and possibly of the stem cell of the neoplasm itself.[31, 32] It has thus gone some way toward an understanding of why such a group of women is so predisposed. In the more recent course of this research a general theory of neoplasia has been constructed,[33] some elements of which enable a hypothesis to be proposed on the reasons for the exist-

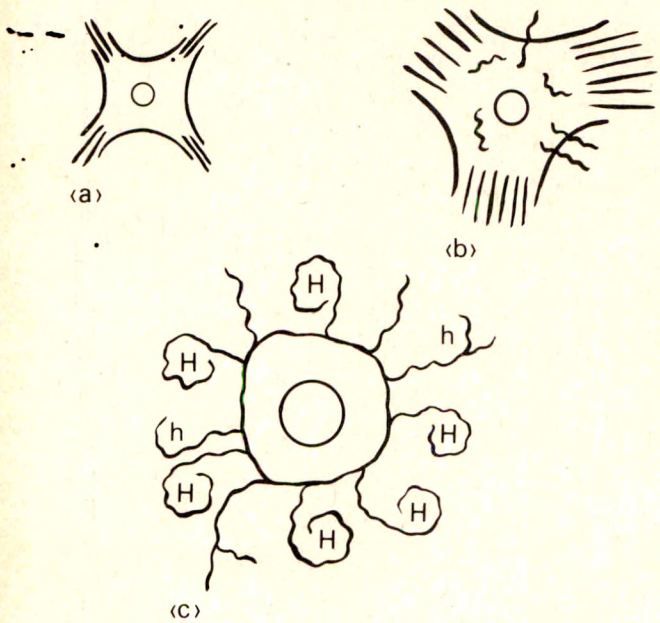


Fig. 1. Arrangement of surface filaments of the normal *(A)* and cancerous *(B)* cell as theoretically predicted.[31] It is proposed that histones of sperm origin *(H* in *(C))* in the environment of the differentiating metaplastic cell rapidly evoke the appearance of excessive DNA-containing filaments at its surface and these specifically determine its neoplastic destiny. Different males may have qualitative or quantitative differences in their gamete histones *(H, h)* of more or less efficacy in the proposed reaction.

ence of males more prone to produce an associated cervical cancer in their sexual partner.

Role of cell surface DNA

The evidence for such a theory is documented elsewhere,[33] but its essentials can be summarized as follows:

1. The majority of the DNA of the eukaryote cell possesses a base sequence fitting it for the combined function of cytoskeleton and environmental sensor. The minor portion of the cellular DNA has a base sequence which is more suitable as a code for the synthesis of amino acids by the familiar transcription-translation mechanism.

2. At any given time a very small fraction of the total cellular DNA, probably less than 1 percent, exists throughout the cytoplasm and also on the surface of the cell in the form of a deoxyribonucleoprotein network.

3. The reservoir for this surface network is the nucleus from which its component filaments are drawn to this site during cellular differentiation by the familiar process of ameboid movement. This ameboid activity by the differentiating cell represents a piecemeal exposure of the genome to the cellular ambient environment whereby a small but specific fraction of the DNA available in the reservoir is selected. Integration of this fraction with the environment both retains it outside the nucleus as a superficial network and programs it for the activation of the protein-synthesizing component of the cellular DNA. This network with which the protein-synthesizing-function DNA is proposedly colinear is thus a type of selective switch. The coincidence of proportionate amounts of these two functional types of DNA, namely, switchgear and protein-synthetic, results respectively in the production of both the mucoid coat (glycocalyx) and the cytoplasmic coat of the differentiated cell. Early in the differentiation process, DNA not so utilized retreats to the nucleus where it is insulated from further activation by the cytoplasmic and mucoid coats.

4. Carcinogens in the cell environment cause the projection by a variety of mechanisms of disproportionately increased amounts of sensory or switchgear type DNA toward the cell surface followed by its subsequent retention in this site (Fig. 1, *A* and *B*). Two end results are thereby made possible: (1) an increased potential for activation of that DNA fraction concerned with protein synthesis and (2) alteration in the surface properties of the cell contingent on an increased content of surface DNA.

Induced modification of surface DNA by histone

For several reasons we have incriminated basic proteins of the sperm head as those substances in the environment of the stem cell of the metaplastic process which are capable of evoking an excessive amount of the DNA of the metaplastic cell to the cell surface.[31] The idea was based on the avidity shown by molecular DNA in vitro under the electron microscope to aggregate and become densely concentrated on films of polystyrene containing histone as contrasted with the behavior of these molecules on films containing other proteins.[34] Proceeding from such studies to the use of histones in cell cultures it was found that a few minutes' contact with low doses (50 to 100 μg per milliliter) of histone but not with other proteins (e.g., albumin, globulin, gelatin) resulted in the enlargement of the nucleus with the production of an extensive mucoid coat which resulted in cell aggregation (Fig. 1, *C*).[35] Such a mucoid coat was shown in previous studies to contain a DNA skeleton derived in turn from the cell nucleus.[36] Hamster kidney cells exposed to low doses of histones behave in the same way with nuclear enlargement. Cells so treated show tumorigenic and invasive properties.[37, 38]

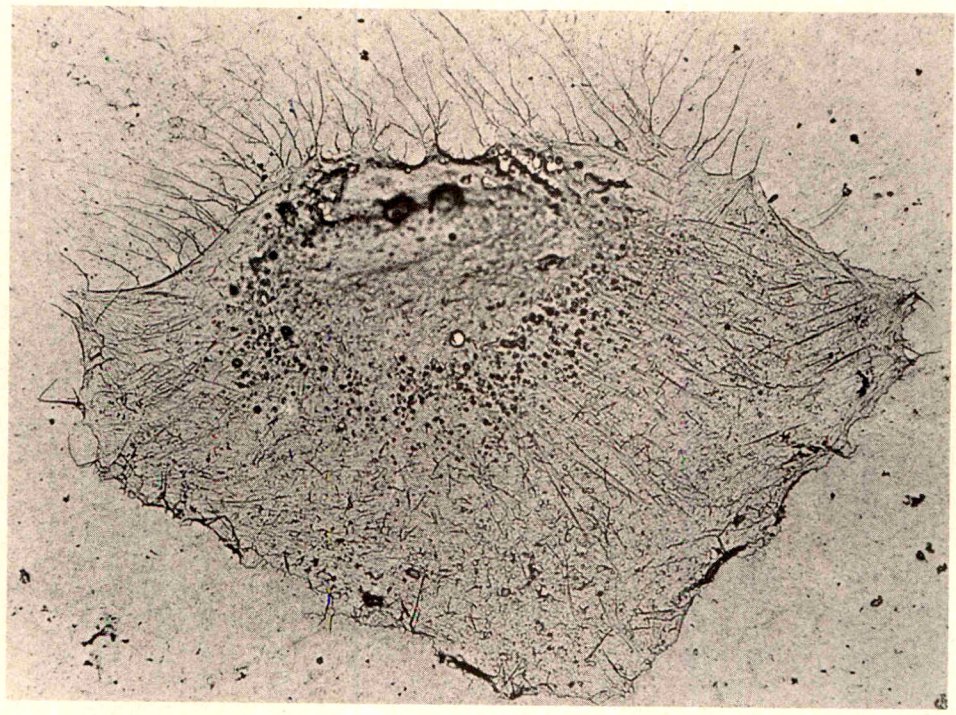


Fig. 2A. Photomicrograph of human melanoma cell from tissue culture rotary shadowed and viewed under the light microscope. The surface coat growing in vitro is extensively covered with microfilaments.[45] Intervening smooth areas of the cell surface are more extensive in normal cells. (×1,000.)

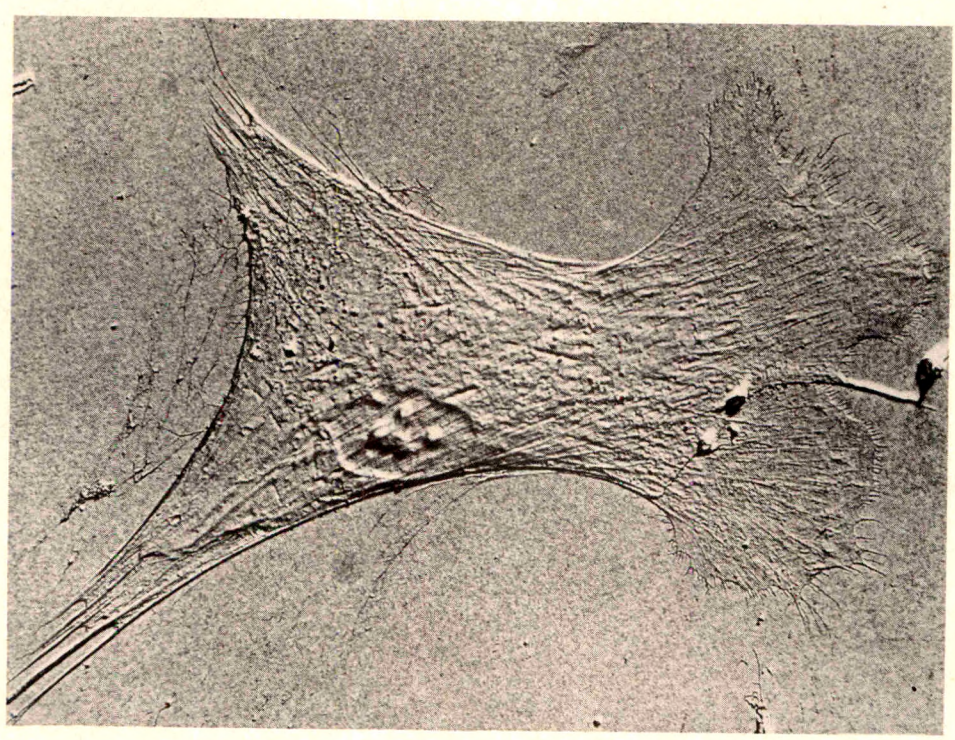


Fig. 2B. Photomicrograph of human colonic cancer cell. See legend of Fig. 2*A*.

Based on a similar argument, the polyamines spermine and spermidine of seminal plasma may be expected to show the same sort of activity as the basic proteins of the sperm head. These basic substances which reach high concentrations in human semen have a similar avidity for DNA.[39]

Comment

Correlation of epidemiological findings indicating the existence of variation among different males with the proposed importance of histones in causing the initial cellular events associated with neoplasia poses the question of the existence of a variation in the content of these basic proteins among the sperm of different males. Histones exist in close association with DNA when the latter is in a condensed state, such as in heterochromatin, and, indeed, vary in linear fashion as the heterochromatin content of the nucleus varies.[40] Not surprisingly, some of the richest sources of very basic proteins are found in association with the condensed DNA of the sperm head.[41] It seems reasonable then to attempt a correlation between quantitative or qualitative variations in sperm histones and those diverse behavioral and sociological attributes of the individual which have been uncovered by epidemiological and other evidence such as occupation group, premature widowhood, and perhaps sexual promiscuity. Methods are available for the extraction of histones from the sperm head[42] and for their further characterization on polyacrylamide gels by electrophoresis[43] which are adaptable to human sperm.[44] It is thus possible to compare both the types and quantities of the sperm histones of partners of known cases of precancerous and cancerous women with a control series. Similar quantitative studies are possible in seeking differences in the basic polyamine content of different semen samples.

At the cellular level it should be possible to add sperm basic proteins to cultures of normal differentiating cells and examine their subsequent fate on reinjection into the host in the same way as Latner and co-workers[38] have done. Hamster kidney cells so treated were shown to produce a tumor upon reinjection which actively invaded host tissues. Evidence of an equally indirect type is afforded by morphological study of the surface coat of histone-treated cells. On theoretical grounds potentially neoplastic cells should be covered by a coat with an increased content of surface filaments (Fig. 1, *B*), a prediction which has been realized in some recent studies both of ours (Fig. 2)[45] and of some American groups.[46]

Variations in the sperm head content of DNA have recently been reported between different strains of mice using cytophotometric means.[47] It is possible that some of this variation is reflected in variations in histone content with which the DNA is associated and this too may be resolvable with cytochemical techniques of the type used for showing quantitative strain difference in histones in plant cells[40] and in the human cervix uteri.[48]

We wish to thank Prof. Martin Vessey and Prof. Sir Richard Doll of Oxford for the constructive and critical comments on the manuscript; Mr. Robert Markham and Mr. Peter Blackwell of Sydney and the editor of *Pathology* for kind permission to reproduce Fig. 2, and for their assistance in many of the studies on which this hypothesis is based.

REFERENCES

1. Rigoni-Stern, D.: Fatti statistici relativi alle mallattie cancrose che servirono di base alle poche cose dette dal Dott. G. Servire, Prog. Pathol. Terap. Ser. **2:** 507, 1842.
2. Rotkin, I.: A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents, Cancer Res. **33:** 1353, 1973.
3. Kessler, I.: Perspectives on the epidemiology of cervical cancer with special reference to the herpes virus hypothesis, Cancer Res. **34:** 1091, 1974.
4. Coppleson, M.: Carcinoma of the cervix: Epidemiology and aetiology, Br. J. Hosp. Med. **2:** 961, 1969.
5. Wynder, E. L., Cornfield, J., Schroff, P., and Doraiswami, K. R.: Study of environmental factors in carcinoma of the cervix, Am. J. Obstet. Gynecol. **68:** 1016, 1954.
6. Reid, B. L.: Cancer of the cervix uteri: Review of causal factors with an hypothesis for its origin, Med. J. Aust. **1:** 375, 1965.
7. Coppleson, M., and Reid, B.: Preclinical Carcinoma of the Cervix, Oxford, 1967, Pergamon Press, p. 254.
8. Reid, B. L., and Coppleson, M.: *In* McDonald, R. M., editor: Scientific Basis of Obstetrics and Gynaecology, Oxford, 1971, J. & A. Churchill, Ltd., p. 415.
9. Beral, V.: Cancer of the cervix: A sexually transmitted disease, Lancet **2:** 1037, 1974.
10. Boyd, J. T., and Doll, R.: A study of the aetiology of carcinoma of the cervix uteri, Br. J. Cancer **18:** 419, 1964.
11. Singer, A.: The male factor in cervical cancer, Oxford Med. Sch. Gaz. **25:** 18, 1973.
12. Singer, A.: Carcinoma of the cervix and herpes virus, Br. Med. J. **3:** 290, 1972.
13. Singer, A.: Cancer of the cervix: A sexually transmitted infection? Lancet **2:** 41, 1974.
14. Singer, A.: Multifactorial Aspects of the Cause and Nature of Cervical Precancer, London, 1975, Edgar-Gentilli Prize Essay, Royal College of Obstetricians and Gynaecologists.
15. Martinez, L.: Relationship of squamous cell carcinoma of the cervix uteri to squamous cell carcinoma of the penis, Cancer **24:** 777, 1969.
16. Feminella, J.: An apparent increase in genital carcinomas

amongst wives of men with prostatic cancer: An epidemiological study, Bull. Clin. Med. **20:** 6 3, 1973.
17. Blythe-Smith, D., and Jenkins, R.: Cervical cancer in a housing project: Report of a cluster of cases, Am. J. Obstet. Gynecol. **104:** 603, 1969.
18. Martin, C.: Marital and coital factors in cervical cancer, Am. J. Pub. Health **27:** 803, 1967.
19. Martin, C.: Marital and Coital Factors in Cervical Cancer, Ann Arbor, Mich., 1967, University Microfilm.
20. Pridan, H., and Lilienfeld, A. M.: Carcinoma of the cervix in Jewish women in Israel 1960-1967: An epidemiological survey, Isr. J. Med. Sci. **7:** 1465, 1971.
21. Ravich, A.: Viral carcinogenesis in venereally susceptible organs, Cancer **27:** 1493, 1971.
22. Kaplan, G., and O'Conor, V.: The incidence of carcinoma of the prostate in Jews and Gentiles, J. A. M. A. **196:** 804, 1966.
23. Kook, N., and Kook, H.: Carcinoma of the prostate in Israel: Preliminary report, Br. J. Urol. **34:** 322, 1962.
24. Steinitz, R., and Costin, C.: Cancer in Israel, Fact and figures, 1960-1966, Jerusalem, 1970, Ministry of Health and Israel Cancer Association.
25. Singer, A., Heitner, C., Coppleson, M., Smith, P., and Reid, B. L.: Unpublished.
26. Aitken-Swan, J., and Baird, D.: Cancer of the uterine cervix in Aberdeenshire: Epidemiological aspects, Br. J. Cancer **20:** 642, 1966.
27. Dorn, H. F., and Cutler, S. J.: Morbidity From Cancer in the United States, Washington D.C., 1959, USPHS Publication No. 590, U.S. Govt. Printing Office.
28. Wynder, E. L.: Epidemiology of carcinoma in situ of the cervix, Obstet. Gynecol. Survey **24:** 697, 1969.
29. Theilhaber and Greischer, 1910: *Quoted by* Kennaway, E. L.: The racial and social incidence of cancer of the uterus, Br. J. Cancer **2:** 177, 1948.
30. Wakefield, J., Yule, R., Smith, A., and Adelstein, A. M.: Abnormal cytological smears, carcinoma of the cervix uteri, and husbands' occupation, Br. Med. J. **2:** 142, 1973.
31. Coppleson, M., and Reid, B. L.: The origin and nature of premalignant lesions of the cervix uteri, *in* Taymor, M. L., and Green, T. H., editors: Progress in Gynaecology, New York, 1975, Grune & Stratton, Inc.
32. Reid, B. L., and Coppleson, M.: The natural history of cervical carcinoma, *in* Jordan, J., and Singer, A., editors: The Cervix, London, 1976, W. B. Saunders Company.
33. Reid, B. L.: Integration of the living cell with its environment: Speculation on the function of the DNA content of surface mucoids, Biosystems **5:** 207, 1974.
34. Reid, B. L., and Blackwell, P. M.: The behaviour of DNA molecules on polystyrene films, Aust. J. Med. Technol. **4:** 168, 1973.
35. Reid, B. L., and Blackwell, P. M.: Histone and polyaminoacid DNA interactions at molecular and cellular levels, Proc. Eighth Int. Congr. Electron Microscopy, Canberra **2:** 270, 1974.
36. Reid, B. L., and Blackwell, P. M.: Nuclear extensions of cultured cells: A possible mechanism of cellular differentiation, *in* Ledoux, L., editor: Informative Molecules in Biological Systems, Amsterdam, 1971, North Holland Publishing Co., p. 285.
37. Latner, A. L., and Longstaff, E.: Transformation of mammalian cells by crude histones, Br. J. Cancer **25:** 280, 1971.
38. Latner, A. L., Longstaff, E., and Turner, A. G.: Enhanced malignant behaviour of cells treated with crude rat histone, Br. J. Cancer **27:** 218, 1973.
39. Tabor, H.: The protective effect of spermine and other polyamines against heat denaturation of deoxyribonucleic acid, Biochemistry **1:** 497, 1962.
40. Himes, M.: An analysis of heterochromatin in maize root tips, J. Cell Biol. **35:** 175, 1967.
41. Bloch, D. P.: A catalog of sperm histones, Genetics **61:** suppl. 93, 1969.
42. Coelingh, J. P., Rozijn, T. H., and Monfoort, C. R.: Isolation and partial characterisation of a basic protein from bovine sperm heads, Biochem. Biophys. Acta **188:** 353, 1969.
43. Panyim, S., and Chalkley, R.: High resolution acrylamide gel electrophoresis of histones, Arch. Biochem. Biophys. **130:** 337, 1969.
44. Reid, B. L.: Unpublished.
45. Markham, R., Blackwell, P. M., and Usher, G.: A shadow-casting technique for the examination of the surface topography of cultured cells, Pathology **7:** 45, 1975.
46. Kalata, G. B.: Microvilli: A major difference between normal and cancer cells, Science **188:** 819, 1975.
47. Moore, G. P. M., and Beatty, R. A.: The DNA content of spermatozoa from different strains of mice, J. Reprod. Fertil. **38:** 473, 1974.
48. Hertzog, R. E.: Zur Bestimmung von Arginin im Zellkern des menslichen Portio Epithels, Arch. Gynaekol. **217:** 437, 1974.

Circulatory and cellular immune responses to squamous cell carcinoma of the uterine cervix

WEN TSUO CHIANG
PING YEN WEI
E. RUSSELL ALEXANDER
Seattle, Washington

The sera from 176 patients with cervical cancer were examined by indirect immunofluorescence against cervical cancer cells (imprints of cervical cancer tissue). The mean serum titer in these patients was significantly higher than the titer in two control groups of identical size. These tumor-related antibodies were also higher in titer in sera from a small sample of nine husbands of cancer patients than in 18 control group patients. A cell-mediated immune response was studied with the use of leukocyte-migration inhibition from 39 blood specimens, including 23 patients with invasive epithelial carcinoma, five with intraepithelial carcinoma of the uterine cervix, six with other gynecologic diseases, and five withou gynecologic disease. Migration inhibition was demonstrated for squamous cell carcinoma of the uterine cervix, suggesting a common specific cell-mediated response.

A NUMBER OF clinical and experimental studies have established the existence of immunologic host responses against tumor in certain human cancers, including melanoma,[1, 2] Burkitt's lymphoma,[3, 4] neuroblastoma,[5] and osteogenic sarcoma.[6] For cervical carcinoma, Goldstein and associates[7] have demonstrated cervical cancer antigen in 16 patients with invasive carcinoma, with the leukocyte-migration–inhibition test. DiSaia and colleagues[8] also showed cell-mediated immunity to certain human malignant cells. Similar results were obtained more recently by Chen and co-workers,[9] who studied 16 patients with homologous and heterologous tumor extracts and cytotoxicity with homologous and autologous cell lines. Evidence of cellular hypersensitivity was very common by all methods.

From the Department of Obstetrics and Gynecology, National Taiwan University, School of Medicine and the Hospital, Taipei, Taiwan, Republic of China and the Department of Epidemiology and International Health, School of Public Health and Community Medicine, University of Washington.

Supported in part by Research Grant CA-11703 from the National Cancer Institute.

Received for publication October 6, 1975.

Accepted February 3, 1976.

Reprint requests: Dr. Wen Tsuo Chiang, Department of Epidemiology (SC-36), School of Public Health and Community, Medicine, University of Washington, Seattle, Washington 98195.

The purposes of these initial studies of cervical cancer antigen are twofold. First, circulatory antibody in this disease has not been well studied. The initial crude method selected was the measurement of circulatory antibody by indirect immunofluorescence. In regard to the examination of cell-mediated response, this study went beyond prior studies in that it examined the relationship of the cell-mediated response to the clinical staging of disease.

Material and methods

Immunofluorescent studies. Cancer patients and control subjects represent a portion of a larger case-control and cohort study of cervical cancer being carried out in Taipei, Taiwan. Patients are from the clinics of National Taiwan University Hospital. Sera from 176 cancer patients and two control groups of equal numbers of women were investigated. The distribution of the clinical staging of the disease is shown in Table I. Control Group 1 consisted of other patients without cancer attending gynecology clinics in the same hospital, matched only for age, while Control Group 2 was matched for age, husband's education, age at marriage, parity, and presence or absence of pregnancy at the time of study. Sera of 27 patients and the two matched control groups of equal numbers were tested against cervical cancer antigens from four different sources for reproducibility of the serum titer

Table I. Number of sera from patients or control subjects of the highest dilution which reacted to the indirect immunofluorescence test against imprints of cervical squamous cell carcinoma antigen.

Group	Clinical staging	Serum dilution <1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	Total	GMT
Study group	Stage 0	0	0	2	3	5	6	1	0	1	18	78
	Stage 1	0	1	5	6	12	13	9	3	2	51	95
	Stage 2	0	1	3	5	15	9	8	0	1	42	82
	Stage 3	0	0	5	11	20	17	4	5	2	64	85
	Stage 4	0	0	0	0	1	0	0	0	0	1	
	Total	0	2	15	25	53	45	22	8	6	176	86
Control Group 1	Noncancer, age control	10	9	32	46	44	22	7	5	1	176	38
Control Group 2	Noncancer, full control	26	17	23	34	36	20	9	1	0	176	21

p < 0.006 (Study group vs Control Group 1); N.S. (Control Group 1 vs Control Group 2); p < 0.025 (Stage 3 vs Control Group 1); p < 0.05 (Stage 4 vs Control Group 1); N.S. (Stage 0, Stage 1, Stage 2 vs Control Group 1)

Imprint of cancer antigen used in titration: Antigen A. GMT: Geometric mean titer. N.S.: Not significant.

Table II. Titration of sera of patients and matched control subjects against four different cervical cancer antigens

Group	Antigen A	B	C	D
Cancer patients (No. = 27)				
Geometric mean titer	188	122	122	122
Standard deviation	3	4	3	3
Noncancer—age control (No. = 27)				
Geometric mean titer	29	32	30	36
Standard deviation	3	3	2	2
Noncancer—full control (No. = 27)				
Geometric mean titer	19	18	18	19
Standard deviation	4	4	4	4

Negative controls: (a) human diploid cells and (b) phosphate buffer instead of human sera.

and cross-reaction between the serum and cancer antigen (Table II). All of the cancer patients contributed sera at the time of the initial entrance into the hospital for treatment. None had received prior transfusions. Sera from the husbands of nine of the 176 cervical cancer patients were also studied (Table III). For titration, sera of the cancer patients and the two control groups were coded and examined "blindly" by the laboratory.

Antigen preparation. Fungating tumors were removed before initiation of cancer treatment. Only specimens from patients with blood type O were selected. The amputated tumors were immediately transferred to the laboratory and were lightly touched to the surface of clean glass slides for preparation of the imprints. The imprints were air dried, fixed for 15 minutes in cold acetone (quick frozen), air dried again, and stored at −20° C. The fresh material was inoculated on a diploid human cell line (fetal tonsil [FT]) to determine whether cytomegalovirus or herpes simplex was present. The FT line of human fibroblasts was derived in our laboratory from embryonic tonsillar tissue. Routine cultures of this cell line have never yeilded any Mycoplasmas when inoculated both aerobically and anaerobically.

Indirect immunofluorescence test. Sera were diluted twofold and tested against imprints of tumor antigen, with the use of conjugated antisera specific for human immunoglobulin G* in each test. Serum of serial dilutions was added to appropriate circles of cells on slides (one each) and allowed to stand for 20 minutes at room temperature. The slides were washed in phosphate-buffered saline (PBS) at pH 7.1, rinsed in distilled water, and air dried. One drop of mouse liver powder absorbed conjugated serum was added to the imprints and left on the slides for 20 minutes at room temperature. The slides were then washed with three changes of PBS on a magnetic stirrer. Cover slips were placed over the imprints which were then observed with a fluorescence microscope† (with an HB 200 ultraviolet light source and UG1 and GG13 as the primary and secondary filters). The serum titer was expressed as the reciprocal of the highest dilution of serum showing fluorescence. The site of fluorescence in tumor cells was usually diffusely cytoplasmic, although perinuclear fluorescence was often seen in addition. Cytoplasmic fluorescence was necessary for designation as positive. Whole-cell fluorescence was rarely seen. Human diploid cell lines were treated in the same way, and imprints of cancer cells treated only with PBS were used as controls in each test and were uniformly negative.

*Antibodies, Inc.

†E. Leitz, Inc., Rockleigh, New Jersey 07647.

Table III. Results of the indirect immunofluorescence test on imprints* of cervical cancer against sera of nine patients with cervical cancer, their husbands, and matched control subjects

Study No.	Clinical Stage	Serum dilution†	Husband of patient No.	Serum dilution†	Control Group 1‡	Serum dilution†	Control Group 2§	Serum dilution†
1	III	1:128	1(H)	1:164	10	1:132	19	1:32
2	I	1:128	2(H)	1:128	11	1:16	20	1:16
3	III	1:64	3(H)	1:64	12	1:16	21	1:16
4	I	1:512	4(H)	1:128	13	1:64	22	1:64
5	III	1:256	5(H)	1:128	14	1:64	23	1:32
6	III	1:64	6(H)	1:32	15	1:16	24	<1:8
7	II	1:32	7(H)	1:32	16	1:16	25	1:16
8	III	1:64	8(H)	1:64	17	1:16	26	1:16
9	III	1:32	9(H)	1:16	18	<1:18	27	1:16
Geometric mean titer		94		59		22		20

$P < 0.001$ (spanning Serum dilution† through Control Group 2§)

$P < 0.001$ (spanning Husband of patient No. through Control Group 2§)

$P < 0.01$ (spanning Serum dilution† through Serum dilution†)

$P < 0.01$ (spanning Husband of patient No. through Serum dilution†)

*Imprints: Slide antigen of squamous cell carcinoma of the uterine cervix—Antigen A.

†Serum dilution: Highest dilution of the serum which reacts against imprints.

‡Matched in age only.

§Matched for age, age at marriage, parity, husband's education, and pregnancy.

Cellular immune response studies. Thirty-nine blood specimens were tested for leukocyte-migration inhibition, including five Stage 0, five Stage I, eight Stage II, six Stage III, and four Stage IV cervical cancers and 11 controls. The control group included patients with threatened abortion, ovarian adenocarcinoma, hydatidiform mole, endometrial adenocarcinoma, and uterine fibroids and another group of women without gynecologic diseases. As with the specimens obtained for immunofluorescence study, blood specimens were drawn before initial treatment. No patients had had prior blood transfusions.

The leukocytes from 25 of the 39 cases were challenged by nonautologous cancer antigens, and the remaining 14 were tested autologously.

Antigen preparations. Tissue obtained at cervical biopsy or operation was washed several times with PBS at pH 7.1. The cancer tissue was cut into small pieces with scissors, and 9 c.c. of PBS was added to 1 Gm. of cancer tissue, then ground with mortar and pestle for 30 minutes. The ground homogenized tissue was centrifuged at 1,000 × g for 10 minutes; the sediment was removed, and the supernatant was used as the antigen for the inhibition test.

Separation of leukocytes and leukocyte-migration inhibition assay. The method used in this study was a modification of that of Søborg and Bendixen.[10] Peripheral venous blood (30 and 40 c.c.) was drawn in a heparinized plastic syringe containing 500 U. of sodium heparin (United States Pharmacopeia). Sodium heparin (2 c.c.) (100 U. per milliliter in 0.85 per cent sodium chloride) was added to the drawn blood, and this was transferred to a 500 c.c. centrifuge tube; 1.5 c.c. of polyvinyl pyrrolidine (PVP) was added (solution containing 6 per cent PVP and 0.85 per cent sodium chloride). The tube was then incubated at 37° C. for 1 to 1½ hours. Plasma was aspirated from the tube and centrifugated at 150 × g for 15 minutes. The supernatant was discarded, and 1 c.c. of minimum essential medium (MEM) (containing 0.5 per cent fetal calf serum) was added. The cell suspension was then put through a Dacron column and incubated at 37° C. for 20 minutes. Cells which passed through the column contained 95 per cent monocytes and less than 5 per cent polymorphonuclear leukocytes. The cell concentration was adjusted to 70 million per milliliter by adding 20 per cent fetal calf MEM containing 100 U. per milliliter of potassium penicillin G and 0.1 mg. per milliliter of streptomycin. The cell suspension was centrifuged in capillary tubes (1.5 mm. diameter) at 300 × g, and one end of the tube was sealed with flame. The capillary tubes then were cut at the cell-fluid border and immediately placed in the sterilized Mackaness chambers of 1 ml. capacity (one capillary was in one chamber), one side of which had been sealed with a sterilized cover glass (22 by 22 mm.) by a hot melted paraffin–petroleum jelly mixture. The capillary was anchored firmly with a small drop of silicone grease to

the chamber. The other side of the chamber was then sealed in the same way. One milliliter of 20 per cent fetal calf MEM with or without cancer antigen was injected into the chamber from a side hole. In the antigen-containing chamber, besides 0.7 ml. of 20 per cent fetal calf MEM, 0.3 c.c. of prepared cancer antigen in PBS also was injected. The Mackaness chamber was placed in a horizontally laced Petri dish and incubated for 24 hours at 37° C. The area of migration was measured by a scaled eyepiece under the microscope. The migration in presence and absence of antigen was compared with the following formula:

$$\text{Migration Index (M.I.)} = \frac{\text{area of migration in presence of antigen}}{\text{area of migration in absence of antigen}} \times 100.$$

Results

Immunofluorescent studies. Serum titration against imprints of cancer antigen is shown in Table I. The differences between Control Groups 1 and 2 were not statistically significant (by the chi-square method). The titer of antibody in invasive cervical carcinoma cases differs significantly when compared with Control Group 1 or 2, ($p < 0.05$). This was not true for titers in cases of carcinoma in situ. The mean titer for Stage 0 patients (carcinoma in situ) more nearly resembled the titer of invasive cancer patients than that of the control group but did not differ significantly (by the t test), perhaps due to the small number of patients in the group with carcinoma in situ.

Sera from 27 cervical cancer patients and two matched control groups were titrated against four imprints of cancer antigens (Table II). The mean titer of antibody in cancer patients was higher than in each of the control groups. For each individual, the highest reactive serum dilution was remarkably consistent for the four different carcinoma antigens. These four cancer antigens from Stage II or III epidermoid carcinoma were checked for possible contamination by cytomegalovirus and herpes simplex, but, as with all antigens, no viruses were isolated.

In nine of the patients with invasive cervical cancer who were studied, the sera of the husbands was also collected. The sera of these husbands showed antibody levels similar to those of the patients and differed significantly from Control Groups 1 and 2 (Table III).

Cellular immune response studies. Leukocyte-migration inhibition to cervical cancer antigen occurred in 23 patients with squamous cell carcinoma of the cervix and in five cases of carcinoma in situ (as compared to the migration of the patient's leukocytes in antigen-free MEM). The results were consistent when challenged by either autologous or nonautologous antigen (Fig. 1). The average M. I. values in each clinical stage of cancer are listed in Table IV. The degree of inhibition was positively correlated to the clinical staging in invasive cervical cancer, i.e., peripheral leukocyte sensitivity increased during the next progression of the cancer. The mean M. I. value in five cases of carcinoma in situ challenged by nonautologous cancer antigen was 36.8, a value similar to that of Stage III cervical cancer.

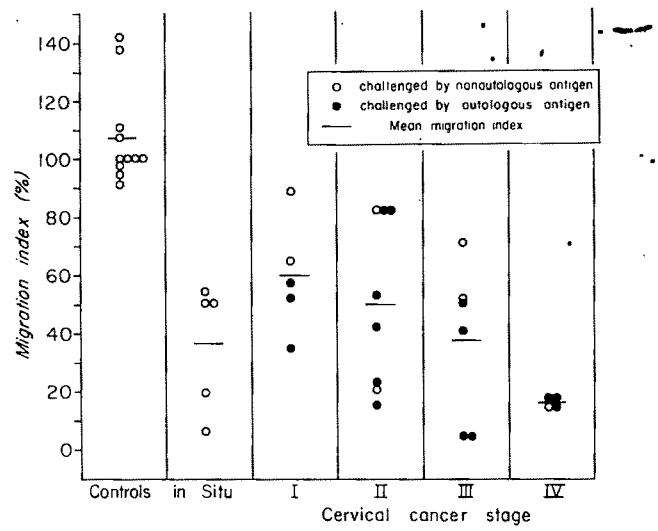


Fig. 1. Inhibition of human leukocyte migration.

Table IV. Results of leukocyte M.I. test for the cases of carcinoma in situ and invasive squamous carcinoma of the cervix challenged with both autologous and nonautologous antigen

Clinical stage	*No. of cases tested*	*Histology*	*Antigen*		*M.I.*	*Average M.I.*
			NA	*AU*		
0	5	Carcinoma in situ	5		36.8	36.8
I	5	Epidermoid carcinoma	2	3	77 48.7	60
II	8	Epidermoid carcinoma	2	6	62 46.3	50.25
III	6	Epidermoid carcinoma	2	4	38 37	37.3
IV	4	Epidermoid carcinoma	3	1	16.7 15	16.2
Total	28					

Mean M.I.: 41.96. S.D.: 25.36. S.E.: 4.79. NA: Challenged by nonautologous antigen. AU: Challenged by autologous antigen.

Two different control leukocyte groups were tested in this study. The first group consisted of five ward nurse volunteers, with no gynecologic complaints. The M. I. value ranged from 91 to 138 with a mean value of 107.2, a value significantly different from that of the patient groups.

A second control group included patients with threatened abortion, ovarian adenocarcinoma, hydatidiform mole, uterine fibroids, and endometrial adenocarcinomas. The M. I. value in this group ranged between 95 and 143 with a mean of 109, a value similar to that of the first tumor-free control group and also significantly different from that of the squamous cell carcinoma patient group ($p < 0.001$ for both—t test).

Comment

Serum antibody against cervical cancer cells was detected in sera of cervical cancer patients and their control groups. Though a significant difference in the antibody level between invasive cancer patients and the control groups was shown, the presence of a cancer-specific circulating antibody was not demonstrated. It is very probable that there is a nonspecific reaction accounting for most of the rather universal antibody detected. That it is more than human cell reaction is suggested by the lack of fluorescence of human diploid (FT) cells. To obtain the necessary number of cellular imprint slides of the normal cervix was deemed too difficult at the time of this study, but this should be evaluated in the future.

The higher antibody titer in the sera of both patients and their husbands suggests that infectious agents could be associated with cervical carcinoma (Table III). We were not able to collect serum from husbands of control patients at this time although such specimens may be obtained later. They should also be examined for these antibodies, but there is no reason to suppose a sex bias exists that would result in antibody values for male subjects that are intermediate between those of female cancer patients and their control group.

A significant elevation of serum antibody titer in carcinoma in situ was not demonstrated in this study. On the other hand, in parallel studies in this laboratory, leukocytes from patients with in situ cancer did not differ from those of patients with invasive carcinoma in the leukocyte-migration test. This may indicate the greater sensitivity, in the early phase of cervical cancer, of a measure of cell-mediated immunity than the measurement of circulating antibody by immunofluorescence. It should be noted that a few patients in the control group had very high levels of immunofluorescent antibody. These patients will be followed to see whether they represent developing cases of cervical cancer.

Leukocytes from patients with squamous cell carcinoma of the uterine cervix were sensitized to tumor antigen preparations as indicated by their effectiveness in inhibiting leukocyte migration. It is presumed that inhibition of leukocyte migration is mediated through the effector activities of sensitive lymphocytes, which have been shown to produce migration-inhibition factors in the presence of antigen.[13] As nonautologous antigens as well as autologous antigens showed inhibition of macrophase migration of the patients (Table IV), this immune leukocyte response seems to be directed toward group-specific types of antigens shared by cervical carcinoma cells.

Cervical squamous cell carcinoma–specific antigen has been demonstrated by cytotoxicity assays[8] and by leukocyte inhibition.[4] In this study, a correlation between the clinical stage of cancer and the degree of leukocyte inhibition was also evident, even with the relatively small number of patients studied. If these preliminary studies are more definitely confirmed, the greater sensitivity of leukocytes (lower M. I. value) in more advanced cases of invasive carcinoma of the cervix might be clinically useful in separating them from localized lesions. Such differentiation might permit better selection of patients for operation.

As no inhibition of leukocyte migration was found for other gynecologic tumors challenged by cervical cancer antigen, there is the suggestion that the host response to cervical squamous cell carcinoma is tumor specific.

The nature of carcinoma in situ of the uterine cervix is still under discussion. Histologically, it is a preinvasive or intraepithelial carcinoma of the cervix. Invasive cervical cancer is frequently preceded by carcinoma in situ for several years.[11] However, it is not clear whether lymphocytes of the host recognize intraepithelial carcinoma cells as well as invasive carcinoma cells of the uterine cervix. This study suggests that host lymphocytes in carcinoma in situ and invasive carcinoma of the cervix react in a similar manner. The nature of intraepithelial carcinoma has also been studied by chromosome analysis.[12] Aneuploidy, characteristic of invasive carcinoma of the uterine cervix, was also demonstrated in some cases of dysplasia and most cases of carcinoma in situ. This report supports the concept that host lymphocytes recognize the cells of carcinoma in situ as well as those of invasive carcinoma and that the in situ carcinoma cells are, in fact, malignant.

REFERENCES

1. Lewis, M. G., Ikonopisiv, R. L., Nairn, R. C., et al.: Tumor specific antibodies in human malignant melanoma and their relationship to the extent of the disease, Br. Med. J. 3: 547, 1969.
2. Morton, D. L., Malmgren, R. A., Holmes, E. C., et al.:

Demonstration of antibodies against human malignant melanoma by immunofluorescence, Surgery **64:** 233, 1963.
3. Klein, C., Clifford, P., Klein, E., et al.: Membrane immunofluorescence reactions of Burkitt's lymphoma cells from biopsy specimens and tissue culture, J. Natl. Cancer Inst. **39:** 1027, 1967.
4. Old, L. J., Boyse, E. A., Oetten, H. C., et al.: Precipitating antibody in human serum to an antigen present in cultured Burkitt's lymphoma cells, Proc. Natl. Acad. Sci. U. S. A. **56:** 1699, 1966.
5. Hellstrom, I. E., Hellstrom, K. E., Pierce, G. E., et al.: Demonstration of cellbound and humoral immunity against neuroblastoma cells, Proc. Natl. Acad. Sci. U. S. A. **60:** 1231, 1968.
6. Priori, E. S., Wilbur, J. R., and Dmochowski, L.: Immunofluorescence tests on sera of patients with osteogenic sarcoma, J. Natl. Cancer Inst. **46:** 1299, 1971.
7. Goldstein, M. S., Shore, B., and Gusberg, S. B.: Cellular immunity as a host response to squamous carcinoma of the cervix. Am. J. Obstet. Gynecol. **111:** 751, 1971.
8. DiSaia, P., Sinkovics, J. G., Rutledge, F., and Smith, J. P.: Cell-mediated immunity to human malignant cells, Am. J. Obstet. Gynecol. **114:** 979, 1972.
9. Chen, S. S., Koffler, D., and Cohen, C. J.: Cellular hypersensitivity in patients with squamous cell carcinoma of the cervix, Am. J. Obstet. Gynecol. **121:** 91, 1975.
10. Søborg, M., and Bendixen, G.: Human lymphocyte migration as a parameter of hypersensitivity, Acta Med. Scand. **181:** 247, 1967.
11. Te Linde, R. W.: Demonstration of the relationship of carcinoma in situ to invasive carcinoma of the cervix, Am. J. Obstet. Gynecol. **115:** 1022, 1973.
12. Jones, H. W., Davis, H. J., Frost, J. K., Park, I., Salimi, R., Tseng, P. Y., and Woodruff, J. D.: The value of the assay of chromosomes in the diagnosis of cervical neoplasia, Am. J. Obstet. Gynecol. **102:** 624, 1968.
13. Bloom, B. R.: Elaboration of Effector Molecules by Activated Lymphocytes. Mediators of Cellular Immunity, New York, 1969, Academic Press, Inc., pp. 247-319.

Outpatient evaluation of patients with atypical Papanicolaou smears: Contribution of endocervical curettage

HUGH M. SHINGLETON, M.D.
HAZEL GORE, M.B., B.S.*
J. MAX AUSTIN, JR., M.D.
Birmingham, Alabama

A series of 603 patients referred with atypical Papanicolaou smears was evaluated by repeat smears, colposcopically directed cervical biopsies, and endocervical curettage. These techniques as a unit can establish an accurate outpatient diagnosis superior to any of these modalities used alone and comparable with findings in conization and hysterectomy specimens. Endocervical curettage has made a unique contribution to the evaluation of such patients; these curettings have allowed examination of tissue fragments and are more reliable in diagnosing neoplasia than are endocervical smears. Invasive carcinoma and its precursors confined to the anatomic endocervical canal can be recognized by this technique, and conversely the absence of neoplastic epithelium in adequate endocervical curettings rules out occult carcinoma. Indications for conization of the cervix are discussed in reference to the other biopsy and cytologic findings, and guidelines are presented for patient management, stressing clinicopathologic correlation and cooperation.

THERE ARE FOUR basic decisions to be made in relation to a cervical lesion: (1) Is it neoplastic? (2) Is it intraepithelial or invasive? (3) What is the distribution of the lesion? (4) How should it be treated? In women with atypical Papanicolaou smears, answers to the first three questions are mandatory before decisions regarding treatment can be made. Conization of the cervix is a time-honored but overused method of assessment of patients with atypical Papanicolaou smears; the recent literature[1–5] advocating the use of colposcopy has pointed out the great savings in time and money achieved by outpatient evaluation with target biopsies. The safety of this procedure has been questioned since with the colposcope only those lesions on the portio and in the lower portion of the endocervical canal can be evaluated. Despite this, advocates of colposcopy have stressed the diagnostic reliability of the techniques,[1, 2, 4, 6] especially if combined with a careful curettage of the endocervical canal. While endocervical curettage has been used for many years and endorsed for its value,[2, 7–10] a comprehensive study examining techniques for processing the specimen, correlation of the specimen with the final tissue diagnoses, and adequacy of the specimen has not been reported. The purposes of this study have been: (1) to assess the accuracy of colposcopically directed cervical biopsies, endocervical curettage, and combinations of these techniques as outpatient procedures by comparing them with the final anatomic diagnosis determined by the addition of findings from conization or hysterectomy specimens on the same patients; (2) to determine which patients should undergo diagnostic conization of the cervix prior to more definitive therapy; and (3) to determine which patients should be treated by outpatient means such as cryosurgery or excisional biopsy.

From the Departments of Obstetrics and Gynecology and Pathology, University of Alabama Medical Center.

Received for publication November 17, 1975.

Accepted January 30, 1976.

Supported by National Cancer Institute Research Grant CA 13148 and by the Comprehensive Cancer Center, University of Alabama Medical Center.

Reprint requests: Dr. Hugh M. Shingleton, Department of Obstetrics and Gynecology, University of Alabama, University Station, Birmingham, Alabama 35294.

**Present address: Rochester General Hospital, Rochester, New York.*

Material and methods

In January, 1970, a Colposcopy Clinic was established at the University of Alabama in Birmingham.

During the following four and a half years, 684 patients with Abnormal Papanicolaou smears were evaluated. Most of the patients (80 per cent) were referred from the Public Health Clinics in Jefferson County, Alabama; the other patients were referred by private physicians.

Most colposcopic examinations were performed by resident physicians under the direct supervision of a gynecologic oncologist. Each of these resident physicians had attended a colposcopy course and had had experience in cervical clinicopathologic correlation.

At the initial visit to the clinic, separate smears were taken from the portio vaginalis (exocervix) with a wooden spatula and from the endocervix, initially by aspiration and thereafter by a cotton swab to compare the techniques.[11] A colposcope was used to survey the cervix (portio and distal endocervix) and upper vagina for atypical areas, as described in the standard colposcopic atlases,[12, 13] and such areas were biopsied. In all patients included in this study, the endocervical canal was curetted with a Kevorkian endocervical curet. For this reason, no pregnant patients were included.

Initially the biopsy material was handled as described by Richart[14]: the biopsies and endocervical curettings were placed separately on clean dry corks, each cork was inserted in a specimen bottle of formalin, and then the bottle was gently inverted. This method allows the pathologist to orient the biopsies which fix flat on the cork and to transfer the curetted material which fixes as a single bolus on the cork. At a later time, the technique was modified with placement of both the biopsies and curettings on small squares of paper towel. This was done initially because dry, clean, intact corks were not always available and continued because it was simple and consistent. It was particularly valuable for endocervical curettings because they continue through the processing up to embedding in the same piece of paper towel, minimizing tissue loss.

After eliminating the pregnant patients and patients without adequate cervical biopsies and endocervical curettings, the final study group consisted of 603 patients. Of these, 168 also had conization of the cervix or hysterectomy or both.

The age range of patients was 14 to 85 years, the majority being under 30 years (Table I). Sixty-nine per cent were black, and 31 per cent were white.

The Papanicolaou smears, endocervical curettings, and cervical biopsies from the Colposcopy Clinic and the referring smears were carefully studied and correlated. At a joint conference between the gynecologic pathologist and the clinicians involved in the Colposcopy Clinic, decisions were made concerning the management of each patient.

Table I. Age distribution of patients

Age group	*Percentage of patients*
14-20	13
21-30	43
31-40	22
41-50	10
51-60	6
61-85	6

When the endocervical curettings were negative (contained fragments of normal endocervical tissue demonstrating adequacy) and focal lesions visible on the anatomic portio were minimal or moderate dysplasia, the patients were usually treated by cryosurgery, with destruction of the atypical epithelium. Such patients were followed thereafter by Papanicolaou smears at three-month intervals. Three consecutive negative smears allowed discharge from the clinic to routine gynecologic care, but the persistence of any atypicality was considered an indication for complete re-evaluation beginning with colposcopic examination. examination.

When the biopsy diagnosis was marked dysplasia or carcinoma in situ and the endocervical curettings were negative, the patients were usually treated by conservative hysterectomy or therapeutic conization, depending upon their desire for future childbearing. Cryosurgery was used as definitive therapy in a few patients if lesions were well defined and good follow-up was assured.

If the endocervical curettings contained only minimally to moderately dysplastic epithelium and careful review of the cervical biopsies and cytologic material suggested no worse than moderate dysplasia, patients were treated with cryosurgery, again provided that careful follow-up was assured.

When the cervical biopsy diagnosis was marked dysplasia—carcinoma in situ and the endocervical curettings were positive (containing fragments of dysplastic or neoplastic epithelium), or when the cervical biopsy was "questionably" invasive, or when referring or clinic smears suggested a diagnosis much more serious than that made from the tissue, conization of the cervix was performed to determine the nature and extent of disease.

When a diagnosis of microinvasive carcinoma was made on a conization specimen, the patient was treated by simple hysterectomy. Patients with diagnoses of invasive carcinoma were managed appropriately by surgical or irradiation therapy.

With the use of these rules for patient management, 85 per cent of patients were managed in the outpatient

Table II. Classification of endocervical curettage

Classification	*Histologic findings*
Curettage diagnosis negative	Mucus, blood, inflammatory cells, columnar epithelium, fragments of endocervix, squamous metaplasia, strips of squamous epithelium, endometrial tissue
Minimal-moderate dysplasia	Strips of minimally or moderately dysplastic squamous epithelium, squamous metaplasia with minimal or moderate dysplasia, poorly oriented dysplastic epithelium at least minimally to moderately dysplastic
Marked dysplasia–carcinoma in situ	Well-oriented strips of markedly dysplastic epithelium or carcinoma in situ with no suggestion of a more atypical lesion
Questionably invasive carcinoma	Strips and nodules or irregular sheets of dysplastic or neoplastic epithelium highly suggestive of invasive carcinoma but without definite evidence of stromal invasion
Invasive carcinoma	Squamous cell carcinoma definitely invading stroma, large papillary squamous epithelial fragments only explained by invasive carcinoma

Table III. Positive endocervical curettings related to age and race of patients

Age group	*White (% with positive curettings)*	*Black (% with positive curettings)*
14-30	13.7	8.9
31-50	39.1	37.7
>50	55.6	55.9
All ages	27.1	21.5

clinic and only 15 per cent required hospitalization for conization of the cervix prior to making a decision regarding definitive therapy. From the inception of the clinic, abstract forms were used to allow keypunching for future analysis. The data for this study were accrued within this record-keeping system which allowed easy retrieval and correlation.

Usual pathologic nomenclature has been utilized to describe the histologic material, with the addition of the definition of microinvasion approved by the Society of Gynecologic Oncologists in January, 1974. "A microinvasive lesion should be defined as one in which neoplastic epithelium invades the stroma in one or more places to a depth of 3 mm. or less below the base of the epithelium and in which lymphatic or vascular involvement is not demonstrated.[15] It might be observed by pathologists that "below the base of the epithelium," presumably surface epithelium, and also presumably meaning epithelium of "usual" thickness (8 to 10 cells?), is a little ambiguous. Therefore, in the practical assessment of these specimens for uniformity, the depth was measured from the surface of the epithelium with the use of a clear plastic ruler superimposed upon the slide. Therefore, the "microinvasion" was slightly less than the definition. In no specimen was an "invasive" diagnosis made on an additional 0.5 mm. of invasion; the specimens did not seem to fall into that category. Indeed, the shallowest invasive carcinoma was confluent and 4 mm. in depth. Confluent lesions, as described by Boyes and associates,[20] were considered and treated as invasive cancer regardless of depth of invasion.

After a number of patients were accumulated in this study, it became apparent that endocervical curettings could be classified precisely, and the nonspecific positive and negative classification should be modified. For this reason all positive endocervical curettings were reviewed and assigned a diagnosis by the criteria outlined in Table II, and such guidelines were used in diagnosis in subsequent patients.

Results and assessment of accuracy of diagnostic techniques

Positive endocervical curettings were found in almost identical percentages of black and white patients, and these percentages increased with increasing age (Table III). The more abnormal the final pathologic diagnosis, the higher the percentage of patients with positive endocervical curettings (Fig. 1).

Three comparisons were made in the subgroup of 168 patients who had conization or hysterectomy or both: (1) comparison of the cervical biopsy diagnosis with the final pathologic diagnosis (Table IV), (2) comparison of the endocervical curetting diagnosis with the final pathologic diagnosis (Table V), and (3) comparison of the "outpatient" diagnosis (cervical biopsy and endocervical curetting diagnosis considered together) with the final pathologic diagnosis (Table VI).

A further analysis was made of the cervical biopsy group in relation to the percentages of patients in whom the cervical biopsy diagnosis equaled or exceeded the final pathologic diagnosis. Among 73 patients whose endocervical curettings were *negative*, cer-

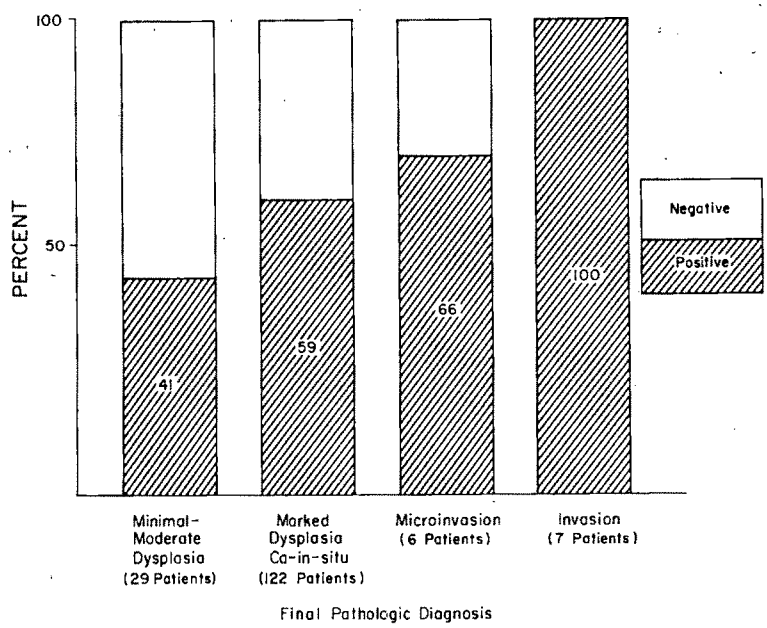


Fig. 1. Endocervical curettage results related to final pathologic diagnosis.

Table IV. Cervical biopsy diagnoses compared to final pathologic diagnoses in 168 patients who underwent conization/hysterectomy

Cervical biopsy diagnosis	*Final pathologic diagnosis*					*Total*
	Negative	*Minimal-moderate dysplasia*	*Marked dysplasia–carcinoma in situ*	*Microinvasive*	*Invasive carcinoma*	
Negative	4	3	10	0	0	17
Minimal-moderate dysplasia	0	26	19	0	1*	46
Marked dysplasia–carcinoma in situ	0	0	93	6	1*	100
Invasive carcinoma	0	0	0	0	5	5
Total	4	29	122	6	7	168

*Significant noncorrelations.

vical biopsy diagnosis equaled the final pathologic diagnosis in 63 (86 per cent). In this group of patients, all but two of the biopsy diagnoses were within one degree of severity for exact correlation with the final pathologic diagnosis. One of these two patients had marked dysplasia in a hysterectomy specimen, and the other had carcinoma in situ in a conization specimen taken because histologic and cytologic findings were not in agreement. None of the patients in this group with negative endocervical curettings had invasive carcinoma, but, among 46 patients with marked dysplasia or carcinoma in situ as the cervical biopsy diagnosis, two had microinvasive carcinoma identified in a conization specimen. No significant error in management would have occurred within this "negative curettage" group had all patients been treated by simple hysterectomy without diagnostic conization.

The correlation of cervical biopsy diagnoses in 95 patients with *positive* endocervical curettings was less accurate. Only 65 (68 per cent) of the cervical biopsy diagnoses were equal to the final pathologic diagnosis. Two patients had a final pathologic diagnosis more than one degree of severity from the outpatient diagnosis; each had invasive carcinoma. One of these had only minimal dysplasia in cervical biopsy material, although endocervical curettings suggested invasive carcinoma, and there was invasive carcinoma in the conization specimen. In the other patient, there was carcinoma in situ in cervical biopsies, questionable carcinoma in the endocervical curettings, carcinoma in situ (probably incompletely removed) in the conization specimen, and invasive carcinoma in the hysterectomy specimen. (Conization is not always an infallible diagnostic technique.)

Table V. Endocervical curettage diagnoses compared to final pathologic diagnoses in 168 patients who underwent conization/hysterectomy

Endocervical curettage diagnosis	*Final pathologic diagnosis*					
	Negative	*Minimal-moderate dysplasia*	*Marked dysplasia–carcinoma in situ*	*Microinvasive*	*Invasive*	*Totals*
Negative	4	17	50	2	0	73
Minimal-Moderate dysplasia	0	12	31	0	1*	44
Marked dysplasia–carcinoma in situ	0	0	31	1	1*	33
Carcinoma in situ–invasive (?)	0	0	0	3	5	18
Totals	4	29	112	6	7	168

*Significant noncorrelations.

Table VI. Outpatient diagnoses* compared to final pathologic diagnoses in 168 patients who underwent conization/hysterectomy

Outpatient diagnosis	*Final pathologic diagnosis*					
	Negative	*Minimal-moderate dysplasia*	*Marked dysplasia–carcinoma in situ*	*Microinvasive*	*Invasive*	*Totals*
Negative	4	2	2	0	0	8
Minimal-moderate dysplasia	0	27	19	0	0	46
Marked dysplasia–carcinoma in situ	0	0	91	3	0	94
Carcinoma in situ–invasive (?)	0	0	10	3	2	15
Invasive	0	0	0	0	5	5
Total	4	29	122	6	7	168

*Based upon both cervical biopsy and endocervical curettings.

Table VII. Final pathologic diagnoses of 17 patients with "negative" cervical biopsies, and positive endocervical curettings

No. of patients	*Endocervical curettage diagnosis*	*Conization or hysterectomy diagnosis*	*Final pathologic diagnosis*
8	Minimal-moderate dysplasia	—	Minimal-moderate dysplasia
1	Minimal-moderate dysplasia	Negative	Minimal-moderate dysplasia
4	Minimal-moderate dysplasia	Marked dysplasia–carcinoma in situ	Marked dysplasia–carcinoma in situ
1	Marked dysplasia–carcinoma in situ	Negative	Marked dysplasia–carcinoma in situ
3	Marked dysplasia–carcinoma in situ	Marked dysplasia–carcinoma in situ	Marked dysplasia–carcinoma in situ

When these three comparisons are considered (Tables IV to VI), it will be noted that four significant errors would have been made had either cervical biopsy diagnosis or endocervical diagnosis alone been accepted as adequate study prior to simple hysterectomy; by using the combined outpatient diagnosis, no error would have been made in patient management.

Throughout the study, cervical biopsy and endocervical curetting diagnoses were considered together as an outpatient diagnosis for therapy planning. Other factors often led to decisions to perform conization or hysterectomy, such as parity of the patient, noncorrelation of the cytologic evaluation with the outpatient diagnosis, lack of follow-up reliability, or desire of the patient for future childbearing (therapeutic conization). Even if these factors are dismissed, however, the outpatient diagnosis could have been used as an accurate measure of the extent of the lesion with immediate simple hysterectomy in every patient other than the 20 with outpatient diagnoses of questionably invasive carcinoma and invasive carcinoma. Thus, outpatient diagnostic accuracy is increased with the use of cervical biopsy and endocervical curetting diagnoses together, and serious errors in management can be avoided.

Of interest is further consideration of a group of 17 patients with negative cervical biopsies but positive endocervical curettings (Table VII). Eight of the 17 patients had outpatient diagnoses of minimal or moderate dysplasia and were treated with cryosurgery; none of these had a conization or hysterectomy and

therefore are not included in the 168 patients in the preceding tables. One patient had an outpatient diagnosis of moderate dysplasia, but there was no lesion in the conization specimen, suggesting that the lesion may have been removed (perhaps only temporarily) by the endocervical curettage. In the hysterectomy specimen from a patient with an outpatient diagnosis of carcinoma in situ, there was no residual lesion. Of four patients with moderate dysplasia, two had carcinoma in situ in a conization specimen and subsequent negative hysterectomy specimens, and the other two had marked dysplasia in a conization specimen and moderate dysplasia in a subsequent hysterectomy specimen. Of three patients with an outpatient diagnosis of carcinoma in situ, one had carcinoma in situ in a hysterectomy specimen (no conization), another had carcinoma in situ in a conization specimen and no residual lesion in the hysterectomy specimen, and the third had carcinoma in situ in the conization specimen (no hysterectomy specimen).

The accuracy and importance of endocervical curettage and its importance in cancer detection were emphasized by the findings in a 53-year-old patient previously mentioned. Because of carcinoma in situ in the cervical biopsy and questionably invasive carcinoma in the endocervical curettings, conization was performed but only carcinoma in situ was diagnosed. Subsequent simple hysterectomy revealed a residual focus of confluent "microcarcinoma" measuring 4 mm. in its greatest depth of penetration and exceeding the limits of microinvasion previously defined. The endocervical curettings had suggested invasion whereas the conization failed to establish the worst diagnosis. The patient received postoperative irradiation although it is possible that she had been cured by the surgical procedure.

Comment

Evaluation of a large series of consecutive patients substantiates the contention that a negative endocervical curettage specimen allows exact diagnosis of cervical cancer by colposcopically directed biopsies.[2] No patient with negative endocervical curettings had invasive carcinoma; two patients (2.7 per cent of those with negative endocervical curettings) had microinvasive carcinoma. Among the patients with positive endocervical curettings 7.4 per cent had invasive carcinoma and 4.2 per cent had microinvasive carcinoma. This rate of invasive lesions found in the positive endocervical curettage group compares with those of Townsend and colleagues[2] (8 per cent) and Tredway and coworkers[1] (12 per cent) in similar patients. The distribution of dysplasia and carcinoma in situ of the cervix and especially the percentage of such lesions apparently confined to the endocervical canal (as determined by postive curettings and negative biopsy) were of interest. In 12 of 29 patients (41 per cent) with minimal or moderate dysplasia, there was involvement of the endocervical canal, compared with endocervical canal involvement in 72 of 122 patients (59 per cent) with marked dysplasia or carcinoma in situ. These are higher than Burghardt's[17] figures of 21.5 and 44.4 per cent respectively, but it is not known whether the age groups in both series are similar. While Richart[18] estimated that 18 per cent of patients with carcinoma in situ had disease limited to the endocervical canal, only 6 per cent of patients in this series had carcinoma in situ only in the endocervical curettings. It is quite likely that the lesions in some of the cervical punch biopsies were from the distal endocervical canal visible to the colposcopist, thus reducing the percentage of lesions found only in endocervical curettings. Also, as suggested in the comparison with Burghardt's[17] series, there may have been age differences.

Table VIII. Indications for conization among patients evaluated by colposcopy and endocervical curettage

1. Cervical biopsies suggestive but not diagnostic of invasive carcinoma
2. Positive endocervical curettings suggesting at least marked dysplasia
3. Circumstances preventing adequate examination by colposcopy and biopsies (e.g., atrophy, stenosis, fibroids)
4. Papanicolaou smears suggesting at least marked dysplasia not explained by colposcopic and tissue findings

The classification of endocervical curettings into degrees of atypicality was found to be practical and helpful. While Griffiths and associates[10] briefly indicated that degrees of atypia might be distinguished in curetted material, a classification was not proposed. Use of such a classification[16] to subdivide patients has permitted direct hysterectomy in patients in whom curettings contained only minimally to moderately dysplastic epithelium. There has not been a significant error to date with this approach. This differs from the claim of Townsend and associates[2] that all patients with neoplastic disease in the endocervical canal require conization of the cervix. Under certain circumstances, however, conization is mandatory for definite diagnosis (Table VIII), although on rare occasions it too may be inadequate, and in patient evaluation all available data must be considered.

Large numbers of patients with diagnoses of minimal or moderate dysplasia were treated by cryosurgery after outpatient evaluation. Although treatment by

cryosurgery is not in the purview of this discussion, as a general rule, only the less marked lesions were treated by such local means because of the failure rates with cryosurgery reported by Tredway and co-workers.[1] In his series, the failure rate was only 10 per cent in patients who had minimal or moderate dysplasia whereas the failure rate was 31 per cent in patients with marked dysplasia or carcinoma in situ. The post-cryosurgery conization studies of Creasman and associates[19] also lend caution to the treatment of carcinoma in situ with the commonly available forms of cryotherapy; nevertheless, carefully selected patients with discrete lesions may be so managed if follow-up is assured.

Minimal variations occurred in the correlation of the cervical biopsies and endocervical curettings with the final pathologic diagnosis. Such variations occurred even when biopsies and curettings were considered for consolidated outpatient diagnosis. However, since "one man's dysplasia is another man's carcinoma in situ," variations of one degree of atypia are not important unless the variation occurs between microinvasive and invasive carcinoma. During a four and one-half year period, 603 patients have been managed satisfactorily by this method, and confidence in it is high at this institution.

It must be remembered when such a method as this is used that patients cannot be evaluated only by written reports from a variety of laboratories. Papanicolaou smears and histologic slides must be considered in conference between the pathologist and the gynecologist with full discussion of clinical features for individual determination of management of each patient.

REFERENCES

1. Tredway, D. R., Townsend, D. E., Hovland, D. N., and Upton, R. T.: Colposcopy and cryosurgery in cervical intraepithelial neoplasia, Am. J. Obstet. Gynecol. **114:** 1020, 1972.
2. Townsend, D. E., Ostergard, D. R., Mishell, D. R., and Hirose, F. M.: Abnormal Papanicolaou smears, Am. J. Obstet. Gynecol. **108:** 429, 1970.
3. Shingleton, H. M.: Evaluation of patients with atypical Pap smears, Ala. J. Med. Sci. **9:** 248, 1972.
4. Thompson, B. H., Woodruff, J. D., Davis, H. J., Julian, C. G., and Silva, F. G.: Cytopathology, histopathology, and colposcopy in the management of cervical neoplasia, Am. J. Obstet. Gynecol. **114:** 329, 1972.
5. Kolstad, P.: Diagnosis and management of precancerous lesions of the cervix uteri, Int. J. Gynaecol. Obstet. **8:** 551, 1970.
6. Ortiz, R., Newton, M., and Langlois, P. L.: Colposcopic biopsy in the diagnosis of carcinoma of the cervix, Obstet. Gynecol. **34:** 303, 1969.
7. Richart, R. M.: Techniques for the detection and diagnosis of cervical neoplasia, *in* Gyn Oncology, International Congress Series No. 203 71-79, Amsterdam, 1969, Excerpta Medica Foundation.
8. Kolstad, P.: Carcinoma of the cervix, Stage IA, Am. J. Obstet. Gynecol. **104:** 1015, 1969.
9. Younge, P. A.: Premalignant lesions of the cervix: Clinical management, Clin. Obstet. Gynecol. **5:** 1137, 1962.
10. Griffiths, C. T., Austin, J. H., and Younge, P. A.: Punch biopsy of the cervix, Am. J. Obstet. Gynecol. **88:** 695, 1964.
11. Shingleton, H. M., Gore, H., Straughn, J. M., Austin, J. M., Jr., and Littleton, H. J.: The contribution of endocervical smears to cervical cancer detection, Acta Cytol. **19:** 261, 1975.
12. Boltan, K. A., and Jaques, W. E.: Introduction to Colposcopy, New York, 1960, Grune & Stratton, Inc.
13. Kolstad, P., and Stafl, A.: Atlas of Colposcopy, Oslo, 1972, Universitetsforlaget.
14. Richart, R. M.: The handling of small tissue samples for pathologic examination, Bull. Sloane Hosp. Women **9:** 113, 1963.
15. Boronow, R. C., Moderator: Symposium: Defining cervical microinvasive carcinoma, Contemp. Ob-Gyn **5:** 122, 1975.
16. Gore, H., Shingleton, H. M., and Austin, J. M., Jr.: A classification of endocervical curettings, Gynecol. Oncol. In press.
17. Burghardt, E.: Early histological diagnosis of cervical cancer, Philadelphia, 1973, W. B. Saunders Company.
18. Richart, R. M.: Colpomicroscopic studies of the distribution of dysplasia and carcinoma in situ on the exposed portion of the human uterine cervix, Cancer **18:** 950, 1965.
19. Creasman, W. T., Weed, J. D., Curry, S. L., Johnston, W. W., and Parker, R. T.: Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia, Obstet. Gynecol. **41:** 501, 1973.
20. Boyes, D. A., Worth, A. J., and Fidler, H. K.: The results of treatment of 4,389 cases of pre-clinical cervical squamous carcinoma, J. Obstet. Gynaecol. Br. Commonw. **77:** 796, 1970.

Volatile constituents of human vaginal secretions

GEORGE R. HUGGINS, M.D.
GEORGE PRETI, PH.D.
Philadelphia, Pennsylvania

Vaginal secretions were serially studied for 44 ovulatory cycles from 12 patients by means of combined gas chromatograph–mass spectrometry to identify small organic volatile compounds. In 10 of these cycles ovulation was documented with plasma radioimmunoassays for progesterone, estrogens, and LH. These secretions contain a complex mixture of acids, alcohols, hydroxyketones, and aromatic compounds. Lactic acid, acetic acid, and urea were found to be present in all patients and underwent sharp cyclical variations in concentration with maxima in all patients occurring at midcycle. Small-chain, volatile C_2-C_5 aliphatic acids which have been shown to induce mating behavior in male rhesus monkeys were found in only four patients. In these patients the above acids were found predominantly at midcycle and during the luteal phase.

THE COMPOSITION and physical properties of cervical mucus, oviductal and endometrial fluids, as well as vaginal cytology and bacteriology have been investigated.[1–5] In addition, many of the changes in the biochemical and physical properties of cervical mucus and vaginal desquaminate have been correlated with known circulating levels of estrogen, progesterone, and gonadotropins.[6, 7]

Recent reports[8–10] focused attention on the volatile, small, organic compounds reported to be normal constituents of the human genital tract. Volatile (C_2-C_5) aliphatic acids first found in the vaginal secretions of subhuman primates are also present in the human being. These particular compounds have been reported to induce mating behavior in sexually experienced male rhesus monkeys via olfactory pathways. Except for the small (C_2-C_5) aliphatic acids, other volatile organic compounds have not been identified in human vaginal secretions, nor has a cyclic variation of these acids with respect to the day of ovulation been documented. The purpose of this study was to characterize the volatile organic materials in human vaginal secretions and to evaluate any variation of these constituents throughout the menstrual cycle.

From the Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, and the Monell Chemical Senses Center, University of Pennsylvania.

This study was supported in part by a grant from the Rockefeller Foundation (RF 72018).

Received for publication August 11, 1975.

Revised December 11, 1975.

Accepted December 19, 1975.

Reprint requests: Dr. George R. Huggins, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, 106 Dulles, 3400 Spruce St., Philadelphia, Pennsylvania 19104.

Methods and materials

Commercially available vaginal tampons were precleaned by extracting organic contaminants from them with chloroform-methanol (85 to 15 v/v) (2 days) and diethylether (2 days). The tampons were then autoclaved, dried in vacuo, weighed, returned to their original holders with nylon gloves, and stored in clean glass bottles. During half the cycles, female volunteers were asked to insert the prepared tampons at bedtime and remove them upon waking. In the other half, tampons were worn for a 6 hour interval during normal daily activity. Collections were initiated following cessation of menses and continued daily through the fourth day of the hyperthermic phase as determined from a subject's basal body temperature (BBT) chart. Thereafter, collection was carried out on alternate days or nights until the onset of the next menses.

Volunteers were recruited from a family-planning program or were hospital employees and students. All were apparently healthy and had a history of normal, regular menses. A complete history and physical examination was performed to detect any systemic or pelvic disease. Each had a Papanicolaou smear, gonococcus culture, hematocrit, urinalysis, and VDRL. Saline and KOH preparations were done to rule out trichomoniasis or candidiasis.

Table I. Organic constituents of human vaginal secretions

	M.W.
Aliphatic acids:	
Acetic	60
Propanoic*	74
N-Butyric*	88
Isobutyric*	88
Isovaleric*	102
2-Methylbutyric*	102
4-Methylvaleric†	116
Myristic	228
Isomyristic	228
Pentadecanoic	242
Isopentadecanoic (T)‡	242
Palmitic	256
Palmitoleic	254
Steric	284
Oleic	282
Linoleic (T)	280
Alcohols:	
N-Dodecanol‡	186
N-Tetradecanol	214
N-Hexadecanol	242
N-Octadecanol (T)	270
Glycols:	
Propylene glycol	76
Ethylene glycol (A)	62
Glycerol	92
Hydroxyacids:	
Lactic	90
Hydroxyketones:	
3-Hydroxy-2-butanone	88
2-Hydroxypropanone (T)§	74
Aromatic compounds:	
(a) Aldehydes:	
Benzaldehyde§	106
Phenylacetaldehyde	120
Furfural§	96
(b) Alcohols:	
Phenol	94
p-Cresol	108
Furfuryl alcohol	98
(c) Acids:	
Benzoic	122
p-Hydroxyphenylpropionic*	156
Salicylic (T)	138
(d) Nitrogen containing:	
Pyridine	79
Indole§	117
Uracil§	102
Lactams:	
2-Piperidone*	99
Sulfur containing:	
Dimethylsulfone	94
Miscellaneous:	
Cholesterol	386
Squalene	410
Urea	60

*Consistently present in detectable amounts in only four subjects.

†Consistently present in detectable amounts in only one subject (see text).

‡A, Artifact; T, tentative identification via GC retention time or mass spectrum.

§Not consistently present in detectable amounts in all subjects.

In all, 44 ovulatory cycles from 12 patients were investigated. In 10 cycles ovulation was documented by a hormonal profile which included plasma estrogens, progesterone, and LH. These assays were performed by the endocrine laboratory in our Department of Obstetrics and Gynecology with previously documented techniques.[11–13] In the remaining cycles, ovulation was assumed from the BBT chart and the onset of the next menses. Subjects were asked to record incidents of sexual arousal or coitus and instructed not to use vaginal deodorants or douches. Tampons were delivered to the laboratory shortly after removal and frozen until analyzed.

Heptanoic acid was added to each tampon as an internal standard just before organic materials were extracted by a continuous, 24 hour extraction with dichloromethane. Each extract was concentrated to approximately 250 μl via rotary evaporation at room temperature. The resultant chromatograms demonstrated that 90 to 100 per cent of the heptanoic acid was consistently recovered. Model experiments using solutions of acetic, propionic, iso- and n-butyric, hexanoic, and lactic acids as well as 3-hydroxy-2-butanone, furfuryl alcohol, p-cresol, 2-piperidone, cetyl alcohol, and indole have been performed. These demonstrated that acetic acid is recovered in 50 per cent yield, lactic in ≃ 75 per cent, and 3-hydroxy-2-butanone in 80 per cent yield. The remaining compounds were consistently recovered in 90 to 100 per cent yield. These compounds are representative of the diverse polarity and volatility of the secretion's constituents. Their recovery in high yields demonstrated the efficiency of the extraction and concentration steps.

The response of the gas chromatograph's flame-ionization detector was determined for each of the organic constituents being quantitated. The amounts of these constituents in each sample was then determined from the quantity of internal standard remaining in the sample's chromatogram.

Chromatography of the raw extract was performed using internal and coinjected standards on 10 ft. by 2 mm 3 per cent XE-60 and 8 ft. by 2 mm., 10 per cent Carbowax 20M glass columns; in addition, a 12 ft. by 2

mm. 3 per cent SE-30 stainless-steel column was employed for analysis of silylated derivatives. These were formed by taking a 30 μl portion of the extract and allowing it to react for 30 minutes with 5 μl of bistrimethylsilyl-trifluoracetamide (BSTFA Pierce Chemicals). Peak areas, as well as the retention times of all constituents, were obtained manually. Identification and routine analysis of the more polar molecules such as lactic acid and urea were performed by first converting them to their trimethylsilyl derivatives.

Chromatographic conditions for each of the respective analyses were as follows: XE-60, 60° C., 2 min., 3° per min. to 120° then 8° per min. to 230°; Carbowax 20M, 50° C., 4 min., 6° per min. to 220° C.; SE-30°, 75° C., 4 min., 6° per min. to 300° C.

Combination gas chromatography-mass spectrometry (GC-MS) was carried out on selected samples with a Perkin-Elmer 990 gas chromatograph interfaced to a Hitachi/Perkin Elmer RMU-6L mass spectrometer via a Watson and Biemann[14] separator. Identifications were confirmed by comparison of mass spectra and GC retention times with those from commercially available samples.

Results

A variety of small organic molecules of varied compound class are found in the vaginal secretions (Table I). Among those compounds found in all subjects, lactic acid, acetic acid, and urea displayed consistent cyclic changes. Cyclic changes in lactic acid were measured during all 44 cycles; changes in acetic acid and urea were measured during 41 cycles from 11 patients and 21 cycles from 8 patients, respectively.

Lactic acid was the major acidic constituent in the secretions of all subjects at the time of presumed ovulation. A consistent pattern was seen in the cyclic variation of lactic acid. During the proliferative phase, a sharp, isolated increase of two- to fivefold lasting 24 hours was seen in 25 of 44 cycles from 3 to 7 days before the presumed day of ovulation. Nine other cycles displayed two to three peaks during the proliferative phase. In those cycles where hormonal profiles were obtained, these proliferative phase increases closely coincided with the onset of the preovulatory increase in circulating estrogens. Following the proliferative phase increase, lactic acid concentration decreased to previous levels.

All cycles displayed an abrupt rise of 24 to 48 hours' duration in the concentration of lactic acid from 48 hours before to 24 hours after the presumed day of ovulation. Thirty-two of the 44 cycles studied displayed the highest or second highest concentration of lactic acid within this time span. This increase was two to six

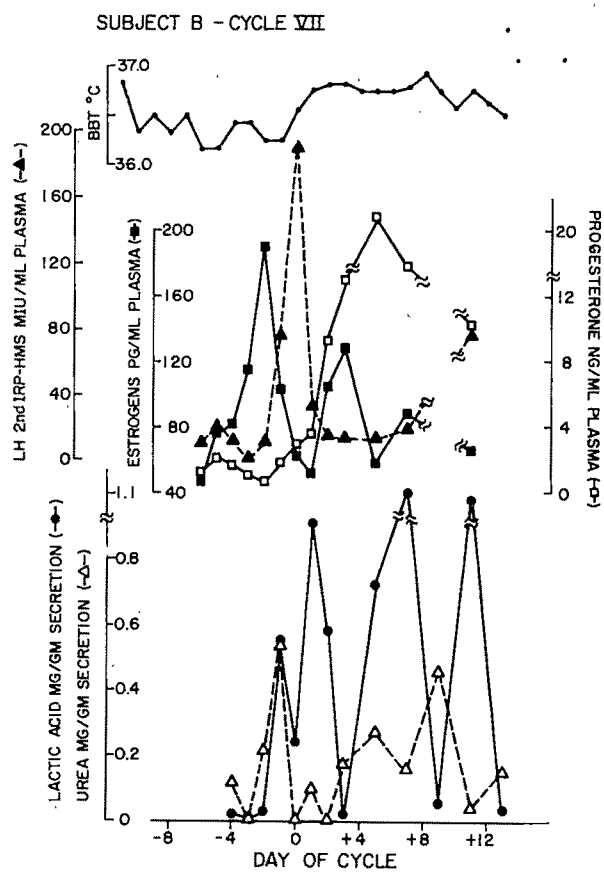


Fig. 1. Changes in LH, estrogens, progesterone, BBT, lactic acid, and urea throughout a cycle from Subject B. Blood was not drawn for each day in the cycle. Prolonged menstruation in this cycle prevented secretion collection from starting before plasma estrogens began to rise. A dual rise in the concentration of lactic acid occurs at midcycle, on days −1 and +1 bracketing the LH surge. Luteal phase maxima are seen on days +7 and +11, the former coinciding with high progesterone levels and the latter occurring just prior to menses. Urea increases to maximum concentration on day −1. A second increase is seen on day +9. Tampons were worn for 6 hours to collect secretions.

times greater than lactic acid concentrations of the 3 previous days. The midcycle lactic acid increase coincided closely with the LH surge. After the midcycle maxima, a decrease in lactic acid was observed in 34 of the 44 cycles studied. During the luteal phase, one or two increases were seen. A rise in lactic acid levels was observed just before menstruation in about 50 per cent of the cycles. Illustrative examples of lactic acid variation in three cycles are shown in Figs. 1 to 3. Cyclic changes in the concentration of lactic acid during cycles monitored only with BBT were similar to those documented with hormonal profiled.

Cyclical changes in the concentration of urea were also measured during 21 cycles from eight subjects.

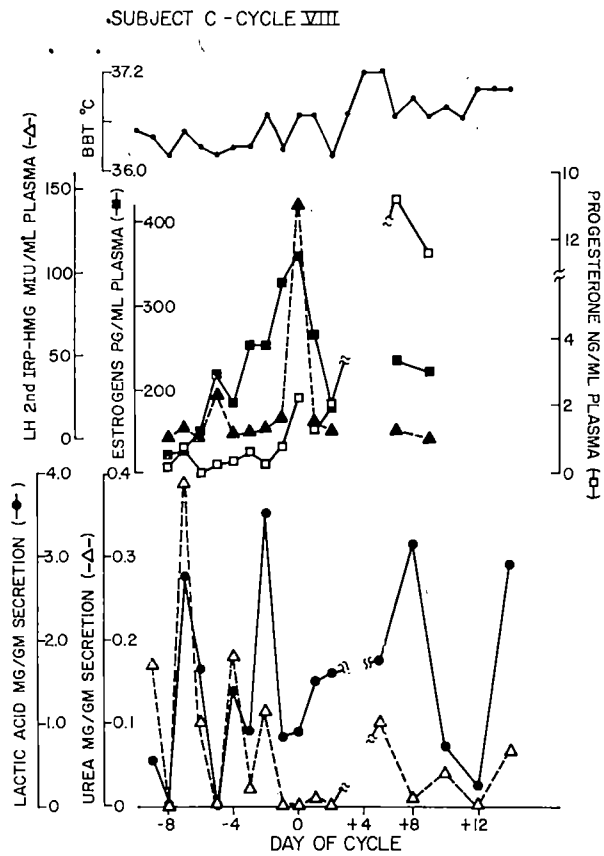


Fig. 2. Changes in LH, estrogens, progesterone, BBT, lactic acid, and urea throughout a cycle from Subject C. Blood was not drawn for each day in the cycle. A proliferative phase rise in lactic acid concentration which occurs just before the onset of the preovulatory increase in plasma estrogens may be seen on day −7. Urea concentration reaches a maximum on this day also. No other larger increases in this compound are seen, although smaller ones are present. The midcycle rise for lactic acid occurs on day −2. A midluteal increase in lactic acid's concentration is seen on day +7, at the time of high progesterone levels. High levels of lactic acid may also be seen on day +13 just before menstruation. Tampons were worn for 6 hours to collect secretions.

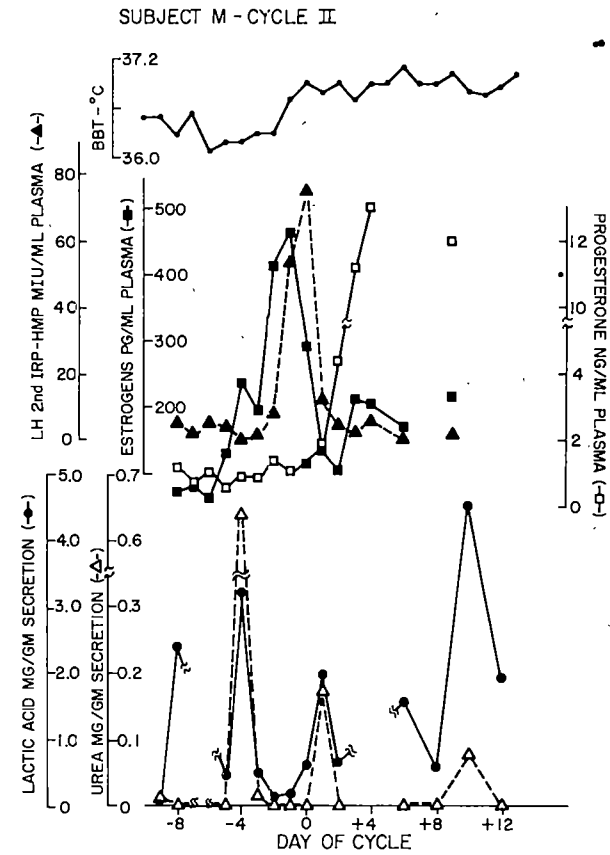


Fig. 3. Changes in LH, estrogens, progesterone, BBT, and lactic acid throughout a cycle from Subject M. Blood was not drawn during each cycle day. Two increases in the concentration of lactic acid are seen in the proliferative phase on day −8 and −4. The latter rise is concomitant with a large increase in urea concentration and closely coincides with the preovulatory increase in blood estrogens. Coincidental increases of both lactic acid and urea concentrations also occur at midcycle (day +1). No large increase in lactic acid was observed during the early or midluteal phase; however, a late luteal phase increase is observed on day +10. Only a small luteal phase increase is seen for urea. Tampons were worn for 6 hours to collect secretions.

An abrupt, isolated proliferative phase increase of 24 hours' duration occurred in 10 of 21 cycles concomitant with, or within 24 hours of the proliferative phase rise in lactic acid. As with lactic acid, urea also increased at midcycle. Distinct, three- to fivefold increases were observed within 24 to 48 hours of the presumed day of ovulation in 14 of the 21 cycles. After this midcycle increase, urea concentration fell rapidly and remained low for several days. As with lactic acid, the luteal phases of each cycle were associated with one or two increases in urea. Examples may be seen in Figs. 1 to 3.

In one cycle (Subject C, Fig. 2), a large simultaneous increase in urea and lactic acid concentration occurred in the proliferative phase. However, no midcycle increase for urea is seen. In another (Subject M, Fig. 3), two proliferative phase increases in lactic acid, 4 days apart, occurred, the latter coinciding with the proliferative phase increase in urea as well as the estrogen surge.

Acetic acid was the only small aliphatic acid identified in all subjects. In 15 cycles, proliferative phase increases were seen. These occurred simultaneously with those of lactic acid in 11 of 15 cycles and were of the same duration. Acetic acid increased at midcycle during 34 of 41 cycles. There were subsequent increases occurring during the luteal phase in 31 cycles.

Maximum concentrations for acetic acid occurred most frequently in the luteal phase (20 out of 41 cycles) or at midcycle (12 of 41 cycles). Examples of the variations in the concentration of acetic acid among subjects throughout the menstrual cycle are shown in Fig. 4.

One subject (L) was found to produce 4-methylvaleric acid. She was one of four subjects who routinely produced more acetic acid than the remaining subjects. These four subjects were the only ones who consistently produced confirmable amounts of C_3-C_5 aliphatic acids. In addition to acetic acid, propionic, isobutyric, *n*-butyric, isovaleric, and 2-methylbutyric acids were found in these subjects.

Data were obtained during a total of 11 cycles from the four above subjects. One produced C_3-C_5 acids only on or after the presumed day of ovulation in each cycle. The other three produced these acids in varying amounts throughout each day of the cycle, with maximum concentrations generally occurring around midcycle and again during the luteal phase. The distribution of the C_2-C_5 acids throughout eight of the 11 cycles from these four subjects is illustrated in Fig. 5. Subjects who produced C_3-C_5 acids also tended to produce more of the following compounds: 2-piperidone, indole, p-cresol, and benzaldehyde. In the remaining subjects, no mass spectrometric confirmation for the presence of C_3-C_5 acids could be obtained.

All data displayed in the figures, except for the plots from Subject D shown in Fig. 5, are from cycles where the tampon was worn for 6 hours. The 6 hour wearing allows for a standardized duration of collection and therefore a better determination of the amount of all organic materials per secretion weight. However, the cyclical changes discussed above were observed with both overnight and 6 hour collection methods.

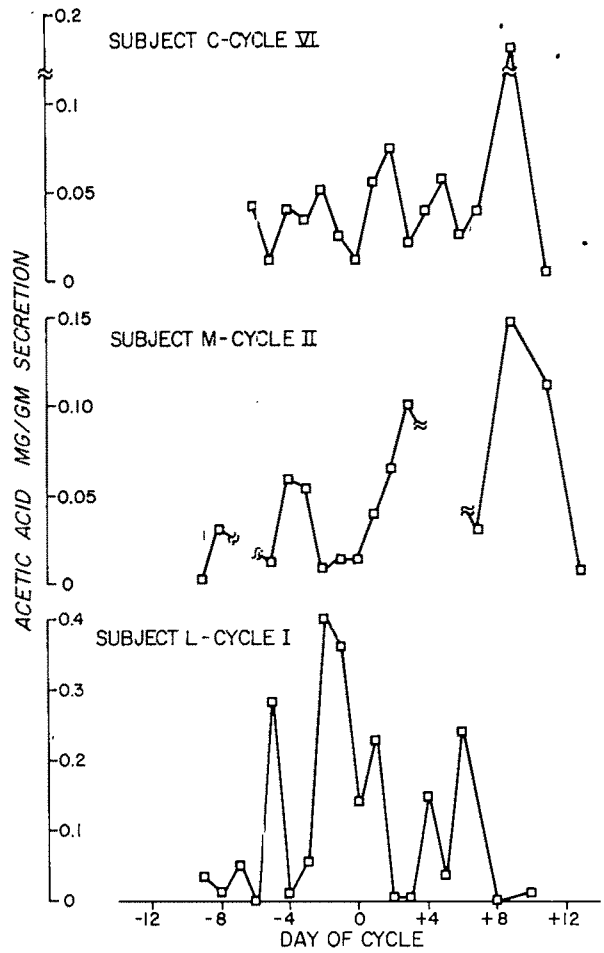


Fig. 4. Changes in the concentration of acetic acid throughout three cycles. Hormonal profiles were obtained during the cycle from Subject M and may be seen in Fig. 3. Proliferative phase increases may be seen in the cycles from Subjects M and L (days −4 to −3 and −5, respectively). Only a small midcycle increase is seen in Subject C's cycle on day +2, whereas a midcycle or early luteal increase is seen on day +3 in the cycle from Subject M. Both M and C show their largest acetic acid concentrations in the luteal phases (both on day +9), whereas the cycle from Subject L has its largest at midcycle (day −2). Tampons were worn for 6 hours to collect secretions.

Comment

Previous investigations of secretions from the human lower reproductive tract have been concerned primarily with type and quantity of inorganic ions, small carbohydrate moieties, and large molecules such as enzymes, proteins, mucins, sialic acids, polysaccharides, glycoproteins, and mucopolysaccharides.[1, 7, 15, 16] The vagina also contains a complex mixture of small organic compounds whose nature and quantity have not been previously explored.

The experimental design employed in this study permitted simultaneous monitoring of a wide number of compounds, of diverse structural type, at the parts per million to parts per billion level, on a daily basis. Although the relationship of many of the small organic molecules reported here to biochemical processes occurring in the vagina have not yet been elucidated, the results obtained thus far indicate that concentration changes in several of these molecules correlate with changing sex steroid levels. In addition, these changes appear to be sharp and marked, in contrast to the gradual changes reported for many of the larger molecules during midcycle.[1, 7] Serially monitored changes in these molecules with the use of gas chromatography may provide an indication of the approximate time of ovulation.

Changes in lactic acid during the proliferative phase appear to be less consistent than those seen at midcycle.

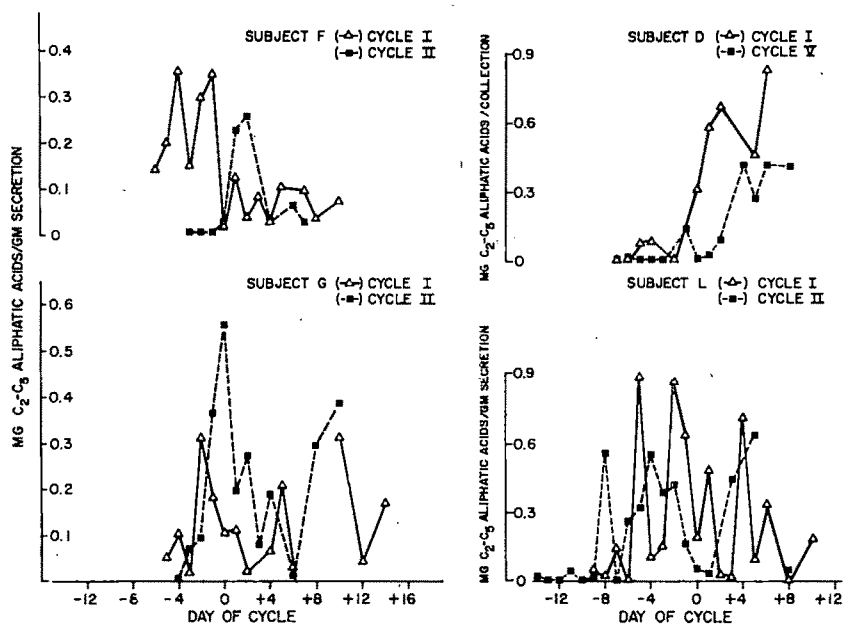


Fig. 5. Changes in the total C_2-C_5 aliphatic acid content of the four subjects who consistently produced them. Maximum acid concentrations were generally observed at midcycle and/or during the luteal phase. Subject L showed proliferative phase maxima whereas D displayed highest concentrations during the luteal phase. Secretions were collected from Subject D while she was sleeping; consequently, data is plotted as MG/collection. Data from cycles employing both collection techniques show the same cyclic variation for all constituents quantitated. Subject L was also shown to produce a C_6 acid (most likely 4-methylhexonoic) which was not detected in the other subjects.

Although 25 or 44 cycles investigated showed single increases in concentration of this compound, another nine displayed multiple (two to three) increases. One of these proliferative phase increases in lactic acid, as well as urea and acetic acid, is related to the initial increase of plasma estrogens as discussed above.

Although little information concerning changes in the biochemistry of the reproductive tract during the early and midproliferative phase has been reported, increases in the concentration of urea, lactic, and acetic acids are indicative of increased biochemical activity at this time. Initial increases in circulating estrogens would be expected to initiate a host of biochemical responses in target tissue including: increased membrane permeability, release of hydrolases from lysozomes, and increased protein, RNA, and DNA synthesis.[15, 17] Consequently, the proliferative phase increases in vaginal organic constituents may be a reflection of initial biochemical events caused by small rises in circulating estrogens.

Many of the identified vaginal constituents may arise as a result of cellular and/or microbiological metabolism. Lactic acid has been assumed to be the principal cause of vaginal acidity for some time.[2] This acid is thought to be produced at least in part by the action of lactobacilli on vaginal glycogen and/or simpler carbohydrates found in the vaginal secretions.[2, 15, 18, 19] Lactobacilli are the predominant microroganisms in the normal human vagina with a number of strains having been reported as present.[2, 19]

Acetic acid may also be formed as a minor product by the same fermentation pathways that produce lactic acid.[20] In addition, the small aliphatic acids, 3-hydroxy-2-butanone and indole, may also be formed by other genera of microflora in the vagina.[21a, b, 22]

Both the vagina and cervix contain enzymes capable of splitting glycogen to glucose.[23] Opinions differ as to whether vaginal glycogen actually increases[2, 24, 25] or undergoes rapid turnover[26] under the influence of increasing estrogens. Recent work by Gregoire and associates[27] suggests the latter. In addition, increases in both vaginal and cervical levels of glucose occur during midcycle.[15, 23] Consequently, increased carbohydrates are available during increasing and/or maximum estrogen estimulation for glycolysis via microflora. Proliferation of the vaginal mucosa under increasing estrogen levels may also yield additional lactic acid from increased cellular glycolysis.[15] However, late luteal phase increases in lactic acid, seen during a majority of the cycles, cannot be accounted for solely on the basis

of increased availability of carbohydrates to microflora or vaginal tissue proliferation due to estrogen stimulation.

The predominant microflora of the vagina do not appear to synthesize urea.[21c] Cyclical changes in urea suggest that human reproductive tract tissue produced urea in response to changes in sex steroid levels. Alternatively, increased estrogens may serve to increase the permeability of the walls of the vagina and allow increased urea levels via transudation. An increase in urea in uterine and fallopian tube fluids under the influence of exogenous estrogen treatment has been reported in the rabbit.[28] Combined estrogen/progesterone administered to these same animals did not produce a significant increase in urea. However, urea in our subjects did show an increase in approximately 80 per cent of the cycles during the mid and late luteal phases. This may be due to urea production in the uterus during the secretory phase as well as increased amino acid and RNA base catabolism during the premenstrual period.

In complex biological mixtures, it is common to find several constituents having very similar or identical gas chromatographic retention times on the same chromatographic column. In such cases, mass spectrometry is needed to elucidate a potentially confusing situation. Such a situation arose in determining which of the subjects produced C_3-C_5 aliphatic acids. Only four subjects consistently displayed confirmable amounts of C_3-C_5 acids. In the remaining eight subjects, GC peaks were seen at retention times identical to those of *n*-butyric acid and the C_5 methyl substituted acids on the Carbowax 20M column. When these peaks were subject to GC-MS analysis they proved to be composed of other compounds, i.e., propylene and ethylene glycol have similar retention times to *n*-butyric acid, whereas phenylacetaldehyde and furfuryl alcohol co-elute at a retention time identical to that of the C_5 methyl substituted acids. In addition, several apparently symmetrical, homogenous peaks in the chromatograms were found to be two compounds when subject to analysis with GC-MS.

During the course of this study, 92 incidents of coitus and/or sexual arousal were reported within 24 hours prior to collection of a sample. Thus far we have not been able to discern any consistent changes in the appearance of the chromatograms collected within 24 hours following these incidents.

In the four subjects who displayed C_3-C_5 acids, the maxima in acid concentration fell either during midcycle or during the luteal phase. A large amount of speculation in both the scientific literature as well as popular press has arisen concerning the possible role odors of C_2-C_5 aliphatic acids may play in human reproductive biology.[29, 30] An in vitro psychophysical evaluation of human vaginal odors by human subjects, throughout a number of menstrual cycles, has shown that these odors do change in pleasantness and intensity throughout the cycle. However, they are not considered as pleasant by human observers.[31]

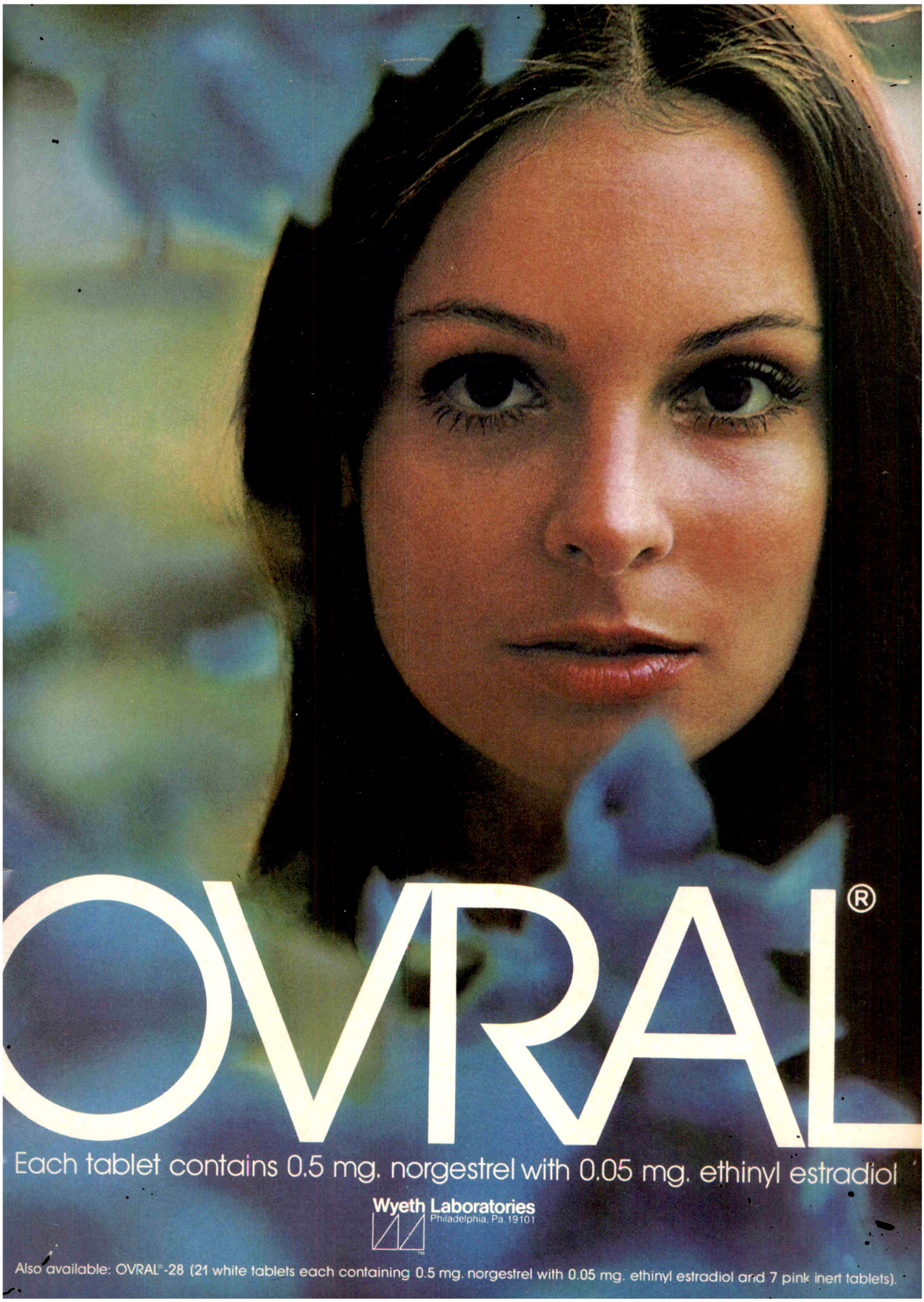
The presence of C_3-C_5 acids in only a small number of our subjects indicates that microbiological and/or enzymatic conditions conducive to their production are not present in all women. In addition, in those women who produce aliphatic acids, large amounts of other compounds were identified. The odors of these volatiles undoubtedly add to and modify the odor produced solely by the C_3-C_5 acids. Given these facts, it is unlikely that volatile acids act alone in a human chemical communication system—given that such a system exists.

We wish to thank Mrs. Jana Bares for her excellent technical assistance. Thanks are also expressed to members of the Monell Center and Obstetrics and Gynecology staff for their comments on the manuscript.

REFERENCES

1. Marshall, J. R.: *In* Uricchio, W. A., and Williams, M. K., editors: Proceedings of a Research Conference on Natural Family Planning, Washington, 1973, Human Life Foundation, Chap. 11, pp. 135-145, and references cited therein.
2. Rakoff, A. E., Feo, L. G., and Goldstein, L.: The biologic characteristics of the normal vagina, AM. J. OBSTET. GYNECOL. **47:** 467, 1943.
3. Brackett, B. G., and Mastroianni, L., Jr.: *In* The Oviduct and Its Function, New York, 1974, Academic Press, Inc., Chap. 5, pp. 133-153.
4. Morris, C. A., and Morris, D. F.: "Normal" vaginal microbiology of women of childbearing age in relation to the use of oral contraceptives and vaginal tampons, J. Clin. Pathol. **20:** 636, 1967.
5. Cohen, L.: Influence of pH on vaginal discharges, Br. J. Vener. Dis. **45:** 241, 1969.
6. Schumacher, G. F.: *In* Blandau, R. J., and Moghissi, K. S., editors: The Biology of the Cervix, Chicago, 1973, The University of Chicago Press, Chap. 11, pp. 201-235.
7. Moghissi, K. S., Syner, F. N., and Evans, T. N.: A composite picture of the menstrual cycle, AM. J. OBSTET. GYNECOL. **114:** 405, 1972.
8. Waltman, R., Tricomi, V., Wilson, G. E., Jr., Lewin, A. H., Goldberg, N. L., and Chang, M. M. Y.: Volatile fatty acids in vaginal secretions: Human pheromones? Lancet **2:** 495, 1973.
9. Michael, R. P., Keverne, B. G., and Bonsall, R. W.: Pheromones: isolation of male sex attractants from a female primate, Science **172:** 964, 1971.
10. Michael, R. P., Bonsall, R. W., and Warner, P.: Human

vaginal secretions: volatile fatty acid content, Science **186:** 1217, 1974.
11. Devilla, G. R., Jr., Roberts, F., Wiest, W. G., Mikhail, G., and Flickinger, G.: A specific radioimmunoassay of plasma progesterone, J. Clin. Endocrinol. Metab. **35:** 458, 1972.
12. Midgley, A. R., Jr., and Jaffe, R. B.: Human luteinizing hormone in serum during the menstrual cycle: Determination by radioimmunoassay, Endocrinology **79:** 10, 1966.
13. Wu, C. H., and Lundy, L. E.: Radioimmunoassay of plasma estrogens, Steroids **18:** 91, 1971.
14. Watson, J. T., and Biemann, K.: Direct recordings of high resolution mass spectra of gas chromatographic effluents, Anal. Chem. **37:** 844, 1965.
15. Gross, M.: Biochemical changes in the reproductive cycle, Fertil. Steril. **12:** 245, 1961.
16. Birnberg, C. H., Wexler, D. J., and Gross, M.: Estimation of ovulation phase by serial tests of cervical and vaginal glucose, Obstet. Gynecol. **21:** 194, 1963.
17. Szego, C. M.: *In* McKerns, K. W., editor: The Sex Steroids: Molecular Mechanisms, New York, 1971, Appleton-Century-Crofts, Chap. 1, pp. 1-52.
18. Masters, W. H., and Johnson, V. E.: Human Sexual Response, Boston, 1966, Little, Brown & Company, pp. 68-100.
19. Wylie, J. G., and Henderson, A.: Identity and glycogen-fermenting ability of lactobacilli isolated from the vagina of pregnant women, J. Med. Microbiol. **2:** 363, 1969.
20. Thimann, K. V.: The Life of Bacteria, New York, 1963, The Macmillan Company, p. 465.
21. (a). Wood, W. A.: *In* Gunsalus, I. C., and Stanier, R. Y., editors: The Bacteria, New York, 1961, Academic Press, Inc., vol. 2, Chap. 2, pp. 67-138. (b) Baker, H. A.: Ibid. Chap. 3, pp. 151-181. (c) Baker, H. A.: Ibid. Chap. 3, pp. 181-203.
22. Sokatch, J. R.: Bacterial Physiology and Metabolism, London, 1969, Academic Press, Inc., pp. 169-175.
23. Fienberg, R., and Cohen, R. B.: Enzymes of glycogen metabolism in the squamous epithelium of the cervix: a histochemical study, Obstet. Gynecol. **31:** 608, 1968.
24. Bo, W. J.: The effect of progesterone and progesterone-estrogen on the glycogen deposition in the vagina of the squirrel monkey, AM. J. OBSTET. GYNECOL. **107:** 524, 1970.
25. Moursi, G. E., Shawky, M. E-F., El-Attar, A. M., Rizk, M. A., and Farid, S.: Cytochemistry of normal vaginal epithelium and under the effect of contraceptive pills in women, Acta Histochem. **39:** 49, 1971.
26. Ayre, W. B.: The glycogen-estrogen relationship in the vaginal tract, J. Clin. Endocrinol. Metab. **11:** 103, 1951.
27. Gregoire, A. T., Kandil, O., and Ledger, W. J.: The glycogen content of human vaginal epithelial tissue, Fertil. Steril. **22:** 64, 1971.
28. Gregoire, A. T., and Rakoff, A. E.: Urea content of the female rabbit genital tract fluids, J. Reprod. Fertil. **6:** 467, 1963.
29. Comfort, A.: *In* Birch, M. C., editor: Pheromones, North-Holland Research Monograph, Frontiers in Biology, Amsterdam-London, 1974, vol. 32, North-Holland Publishing Company, Chap. 20, pp. 386-394.
30. Schneider, R. A.: The sense of smell and human sexuality, Med. Aspects Hum. Sexual. **5:** 157, 1971.
31. Doty, R. L., Ford, M., Preti, G., and Huggins, G. R.: Changes in the intensity and pleasantness of human vaginal odors during the menstrual cycle, Science **190:** 1316, 1975.


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol
Wyeth Laboratories
Philadelphia, Pa. 19101
Also available: OVRAL®-28 (21 white tablets each containing 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol and 7 pink inert tablets).

Two reasons your atrophic vaginitis patient will really appreciate ORTHO Dienestrol Cream:

TRADEMARK

(dienestrol 0.01%)

1 Rapid relief of her symptoms – itching, burning, dyspareunia, discharge



© Ortho Pharmaceutical Corporation

2 Provides economical relief of her symptoms that's easy on her pocketbook...an important consideration if she's on long-term maintenance therapy or a fixed income



Indications: Dienestrol Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases. *Contraindications:* Malignancies or precarcinomatous lesions of the vagina or vulva. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy. *Warning:* Vaginal adenosis has been reported in 30% to 90% of postpubertal girls and young women whose mothers received diethylstilbestrol or a closely related congener during pregnancy. This condition was found most frequently in those cases where DES had been given in early pregnancy (first 12 weeks). The significance of this finding with respect to potential for development of vaginal adenocarcinoma is unknown. Periodic examination of such patients is recommended. *Precautions:* In pruritus vulvae due to infectious conditions, the organism responsible for the infection should be treated with a specific agent. *Dosage:* One or two applicatorsful per day for one or two weeks, then gradually reduced to one-half initial dosage for a similar period. A maintenance dosage of one applicatorful, one to three times a week may be used after restoration of the vaginal mucosa has been achieved. *Supplied:* Available in 2.75 oz. (78 g) tubes with or without ORTHO* Measured-Dose Applicator.

*TRADEMARK

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Ortho

OJ 712-5



She's looking to you for answers. Reassure her.

Results of ten years' clinical experience with Saf-T-Coil® can help you provide the information she's seeking.

Saf-T-Coil is an IUD found comparable to the "pill" in use effectiveness.[1-3] Results of one of the longest investigations—a five-year study[2] in Florida clinics, based on 27,712 insertions and 541,248 woman-months of use—indicate: a low 0.8% *in situ* pregnancy rate, high 80% continuation rate, 11.9% expulsion rate and 8.0% removal rate. Subsequently the investigators made Saf-T-Coil their "device of first choice."

Three Saf-T-Coil sizes ensure contraceptive effectiveness throughout her reproductive years: Saf-T-Coil Nullip 25-S for the nulliparous and young woman, Saf-T-Coil 32-S for the primiparous woman and Saf-T-Coil 33-S for the multiparous woman

Saf-T-Coil Nullip 25-S, in particular, has proved to be a device well-suited to the woman with a small uterus. Results of a separate two-year study[1] in Florida clinics, based on 1,179 insertions and 9,750 woman-months of use, indicate a low 0.4% *in situ* pregnancy rate, relatively high 70% continuation rate, 11% expulsion rate and 19% removal rate—both considered acceptable in nulliparous patients. Insertions were easy and virtually painless, using the standard techniques and no anesthesia. And the Nullip 25-S rapidly accommodates to the shape of the uterine cavity—in contrast to the more rigidly designed devices,which force the uterus to conform. No serious complications were reported in this study.

Every Saf-T-Coil is made of inert plastic with no copper additives.

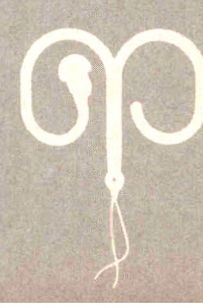
And with every Saf-T-Coil—Saf-T-Sound®—the sterile, disposable intrauterine probe that helps make fitting easier and more accurate.

Caution: Federal law restricts this product to sale by or on the order of a physician.
Contraindications: Should not be used in pregnancy or suspicion of pregnancy, suspicion of carcinoma, acute cervicitis, acute or subacute adnexal disease, fibroids, menorrhagia or unexplained bleeding.

1. Caraway, A. F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A. F. and Vaughn, B. J.: J. Reprod. Med. *10*:171, April 1973.
3. Hayes, O. J.: South. Med. J. *66*:254, Feb. 1973.

Sterile, inert plastic

Saf-T-Coil®



SCHMID LABORATORIES, INC.
LITTLE FALLS, NEW JERSEY 07424

YOU CAN EASE THE BURDEN OF CONSTIPATION OF PREGNANCY

effectively and gently

Suitable for general use in obstetrics[1]
Effective laxation was obtained in 324 (96%) of 336 pregnant women treated with SENOKOT laxatives, as reported in seven published studies,[2-8] with virtual freedom from side effects at proper dosage levels.

Gentle stimulation of peristalsis
Virtually colon-specific, SENOKOT Tablets/Granules provide overnight laxation through gentle neuroperistaltic stimulation of the motor plexus of Auerbach, not by irritation of bowel mucosa. SENOKOT laxatives may be administered with milk and antacids.
Pregnant patients may be started on half the initial recommended dosage of SENOKOT Tablets/Granules, with gradual adjustment to the optimal maintenance dose for regular and comfortable evacuation.

References: 1. Burgess, D. E.: Constipation in Obstetrics, in *Management of Constipation*, edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 179. **2.** Sarles, H., Camatte, R.: *Provence Med* 38:3 (Dec.) 1970. **3.** Scott, R. S.: *Western Med* 6:342 (Dec.) 1965. **4.** Blazy, G.: *Toulouse Med* 64:625 (June-July) 1963. **5.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **6.** Monias, M. B., *et al*: *Md State Med J* 9:439 (Aug.) 1960. **7.** Wager, H. P., Melosh, W. D.: *Quart Rev Surg Obst & Gynec* 15:30 (March) 1958. **8.** Herland, A. L., Lowenstein, A.: *Quart Rev Surg Obst & Gynec* 14:196 (Dec.) 1957.

Senokot laxative claims are documented

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8317 176176

SENOKOT® tablets granules

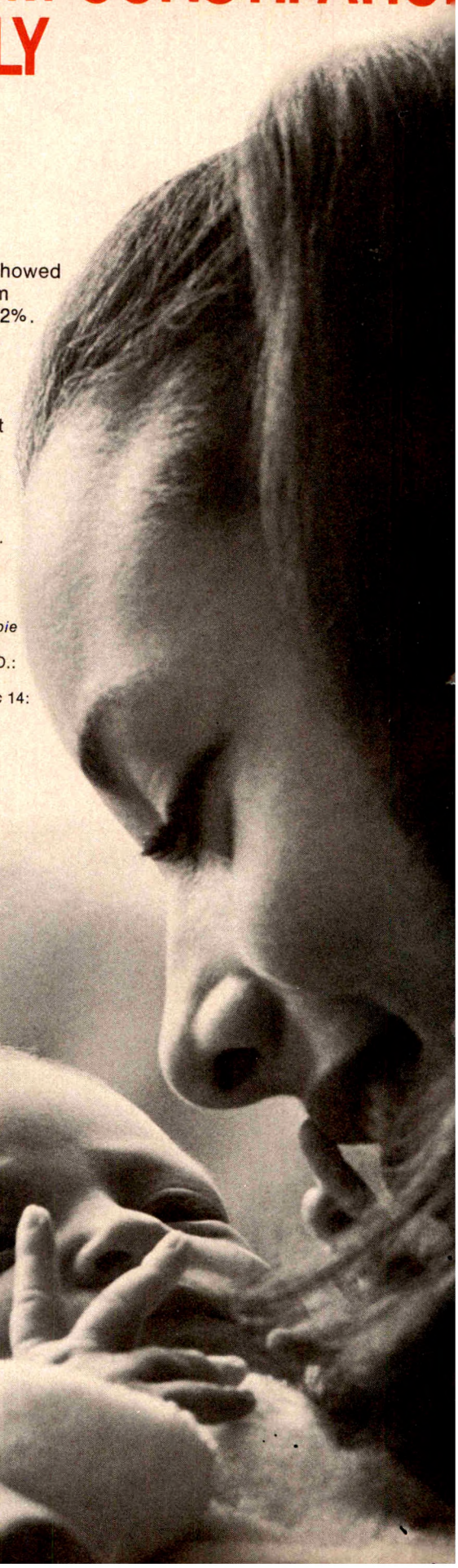
(standardized senna concentrate)

a natural vegetable laxative



TO RELIEVE POSTPARTUM CONSTIPATIO EFFECTIVELY, YET GENTLY

choose a leading laxative in Ob/Gyn practice



Distinguished record of effectiveness

Clinical studies,[2-18] comprising 6,151 obstetric and gynecologic patients, showed that 5,874 or 95.5% responded to SENOKOT laxatives. In 5,527 postpartum patients given SENOKOT laxatives routinely, enemas were used in only 3.2%.

Gentle stimulation of peristalsis

SENOKOT Tablets/Granules are virtually colon-specific,[1] and provide gentle, predictable morning laxation when taken at bedtime. With flexible individualized dosage, you can provide welcome relief for the vast majority of your constipated postpartum patients.

References: 1. Godding, E. W.: Therapeutic Agents, in *Management of Constipation,* edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 65. **2.** Gonzales Genoves, M.: *Rev Bibliografia Med Internac* No. 329 (Nov.) 1968. **3.** Cuevas Leandro, M., Ramirez Varela, E.: *Semana Med de Mexico* 53: No. 742 (Sept. 27) 1968. **4.** Goya, P. A., Perez Vasquez, A.: *Rev Mexico Med* 3: No. 16, 1968. **5.** Monias, M. B.: *Md State Med J* 15:32 (Feb.) 1966. **6.** Scott, R. S.: *Western Med* 6:342 (Dec.) 1965. **7.** Girotti, M., Hauser, G. A.: *Praxis* 53:3 (Dec. 10) 1964. **8.** Baldwin, W. F.: *Can Med Assoc J* 89:566 (Sept. 14) 1963. **9.** Blazy, G.: *Toulouse Med* 64:625 (June-July) 1963. **10.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **11.** Bauer, H.: *Therapie der Gegenwart* 100:528 (Oct.) 1961. **12.** Suarez, J., *et al: Int Rec Med* 173:639 (Oct.) 1960. **13.** Monias, M. B., *et al: Md State Med J* 9:439 (Aug.) 1960. **14.** Kasdon, S. C., Morentin, B. O.: *J Int Coll Surg* 31:455 (April) 1959. **15.** Wager, H. P., Melosh, W. D.: *Quart Rev Surg Obst & Gynec* 15:30 (March) 1958. **16.** Herland, A. L., Lowenstein, A.: *Quart Rev Surg Obst & Gynec* 14: 196 (Dec.) 1957. **17.** Duncan, A. S.: *Brit Med J* 1:439 (Feb. 23) 1957. **18.** Peterson, W. F.: Unpublished report of 2,372 cases of puerperal constipation.

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856

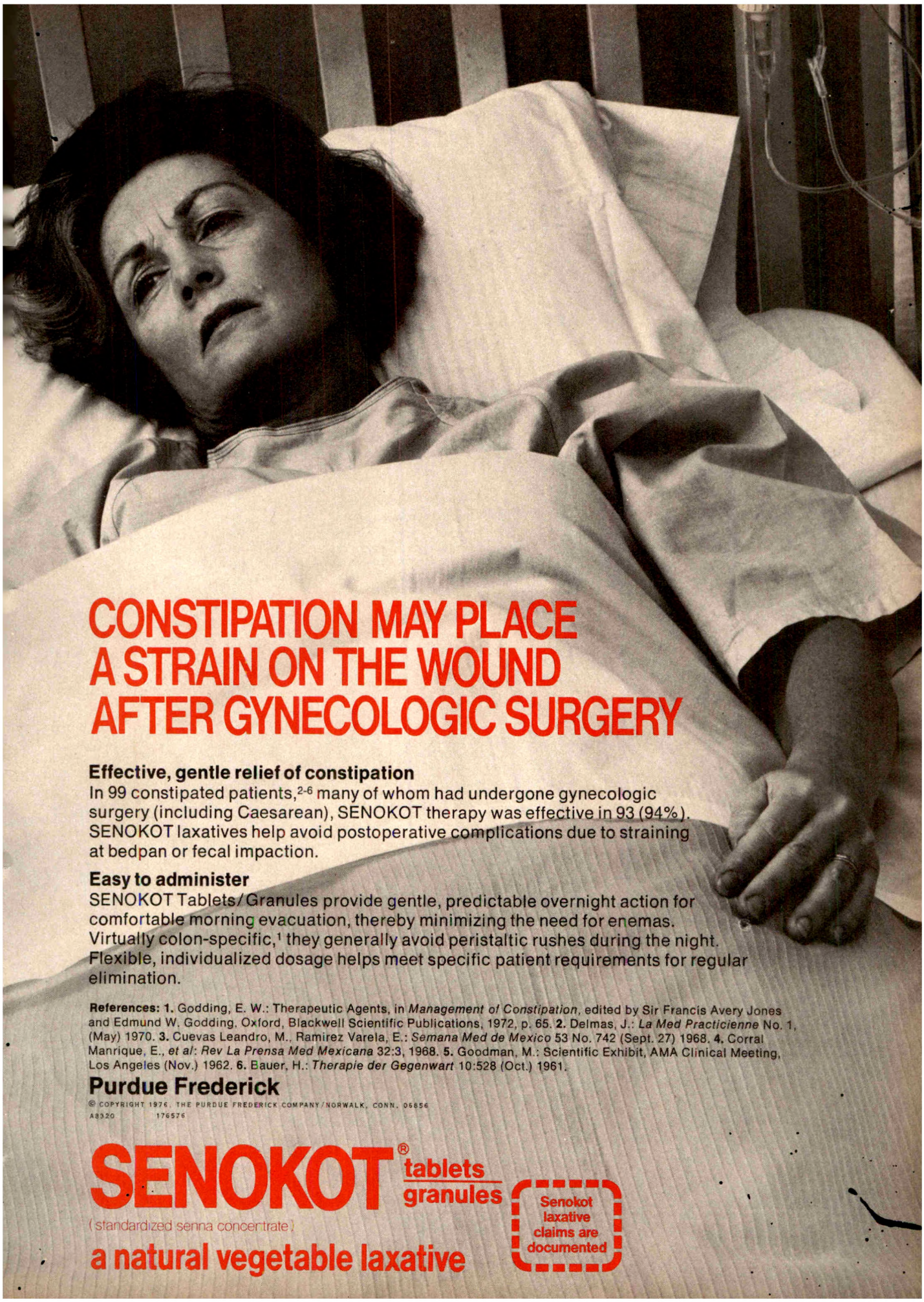
A8321 176676

SENOKOT® tablets granules

(standardized senna concentrate)

a natural vegetable laxative

Senokot laxative claims are documented



CONSTIPATION MAY PLACE A STRAIN ON THE WOUND AFTER GYNECOLOGIC SURGERY

Effective, gentle relief of constipation
In 99 constipated patients,[2-6] many of whom had undergone gynecologic surgery (including Caesarean), SENOKOT therapy was effective in 93 (94%). SENOKOT laxatives help avoid postoperative complications due to straining at bedpan or fecal impaction.

Easy to administer
SENOKOT Tablets/Granules provide gentle, predictable overnight action for comfortable morning evacuation, thereby minimizing the need for enemas. Virtually colon-specific,[1] they generally avoid peristaltic rushes during the night. Flexible, individualized dosage helps meet specific patient requirements for regular elimination.

References: 1. Godding, E. W.: Therapeutic Agents, in *Management of Constipation*, edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 65. **2.** Delmas, J.: *La Med Practicienne* No. 1, (May) 1970. **3.** Cuevas Leandro, M., Ramirez Varela, E.: *Semana Med de Mexico* 53 No. 742 (Sept. 27) 1968. **4.** Corral Manrique, E., *et al*: *Rev La Prensa Med Mexicana* 32:3, 1968. **5.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **6.** Bauer, H.: *Therapie der Gegenwart* 10:528 (Oct.) 1961.

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8320 176576

SENOKOT® tablets granules

(standardized senna concentrate)

a natural vegetable laxative

Senokot laxative claims are documented

On site insight.



2932/2348R746

N-Uristix™



N-Uristix Reagent Strips: Dip-and-read test for nitrite, glucose, and protein in urine. Nitrite test: based on modified Griess reaction; any degree of color reaction is regarded as positive and indicative of at least 10^5 organisms/ml urine. Glucose test: sensitive, specific; glucose oxidase-peroxidase enzyme reaction yields qualitative result in 10 seconds, quantitative result in 30 seconds. Protein test: quantitative, based on well-known "protein error of indicators" phenomenon. Entire N-Uristix test requires 30 seconds to perform, using fresh, well-mixed uncentrifuged urine (preferably first-morning, or bladder-incubated at least 4 hours). Availability: bottles of 100.

Ames Company
Division Miles Laboratories, Inc.
Elkhart, Indiana 46514

In Canada: 77 Belfield Rd., Rexdale, Ontario

The 3 urine chemistries that provide a meaningful profile in screening and monitoring pregnant patients. Glucose: to detect/monitor existent or gestational diabetes. Protein: for an early signal of toxemia and renal dysfunction. Nitrite: a sensitive indicator of significant bacteriuria.

Reliable N-Uristix gives you the information you want. *When* you want it...now. And *where* you want it...in your office. All for less than 14¢ a visit.

Get the insight story. Ask your Ames representative about N-Uristix.

ames

HEALTH INFORMATION THROUGH INNOVATION



Pregnancy can be fun

the well-tolerated iron for the active mother-to-be.

Why Fergon for her iron support? Because it is well tolerated and non-constipating. Fergon is soluble throughout the entire pH range of the g.i. tract and is available for absorption. You can depend on an effective hemoglobin response. Start her on Fergon, and she's getting the three advantages you want in oral iron therapy—excellent tolerance, proven effectiveness, and economy.

the economical name-brand iron recommended by physicians for over 30 years

FERGON®

brand of ferrous gluconate

TABLETS/CAPSULES

Each Tablet contains 320 mg (5 grains) ferrous gluconate equal to approximately 36 mg ferrous iron. Dosage: Adults, 3 to 6 tablets daily; Children, 1 to 3 tablets daily. Supplied: Bottles of 100 and 1000.

Each Capsule contains 435 mg ferrous gluconate equal to approximately 50 mg ferrous iron. Dosage: Adults, one daily or as directed; Children, as directed. Supplied: Bottles of 30.

BREON **BREON LABORATORIES INC.,** Subsidiary of Sterling Drug Inc., 90 Park Avenue, New York, N.Y. 10016

CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and 6 references. Illustrations or additional references require a proportionate reduction in total words.

Placental prostaglandin levels in pre-eclampsia

LAURENCE M. DEMERS, PH. D.
STEVEN G. GABBE, M.D.
Hershey, Pennsylvania, and Los Angeles, California

Pre-eclampsia is characterized by uteroplacental ischemia. Prostaglandins can alter systemic blood pressure as well as regulate blood flow to the fetoplacental unit. In the present study, levels of prostaglandin E were significantly decreased in placental tissue from pre-eclamptic patients. Prostaglandin F, a potent vasoconstrictor, was markedly elevated. These observations indicate that altered placental metabolism of prostaglandins is an important factor in the pathophysiology of pre-eclampsia.

PRE-ECLAMPSIA is a major cause of morbidity and death for the pregnant patient and her fetus. Although the etiology of this disorder is not fully understood, most investigators agree that uteroplacental ischemia plays an important role.[1] Prostaglandins, C_{20} unsaturated hydroxy–fatty acids, are known to regulate placental carbohydrate and steroid metabolism. They may also alter uteroplacental blood flow.[2] We have determined prostaglandin levels in placental specimens from normal and pre-eclamptic patients to assess the role these compounds might play in the pathophysiology of pre-eclampsia.

From the Department of Pathology, The Milton S. Hershey Medical Center, The Pennsylvania State University, and the Department of Obstetrics and Gynecology, Los Angeles County–University of Southern California Medical Center.

Reprint requests: Dr. Laurence M. Demers, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033.

Materials and methods

Randomly selected pieces of fresh placental tissue obtained at delivery were immediately frozen with the use of Freon* and dry ice. Approximately 400 mg. of tissue was collected. The study included 20 women who had undergone normal term spontaneous vaginal delivery. They had not demonstrated hypertension, proteinuria, or edema during gestation. Twenty-two patients with pre-eclampsia were investigated. All were being monitored in the Fetal Intensive Care Unit and demonstrated hypertension—a systolic pressure of 140 mm. Hg (or a rise of greater than 30 mm. Hg) and a diastolic pressure of 90 mm. Hg (or a rise of greater than 20 mm. Hg). Nineteen were found to have proteinuria, and most exhibited edema and/or hyperreflexia. Eight patients met the blood pressure criteria for severe pre-eclampsia. Review of the charts of the

*E. I. DuPont de Nemours & Co., Wilmington, Delaware 19898.

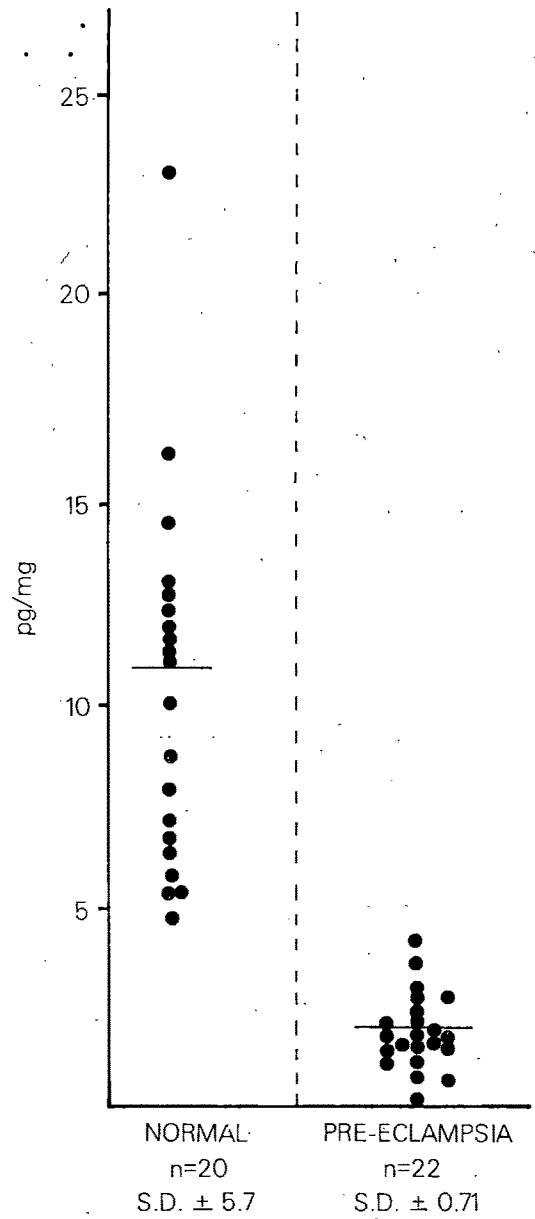


Fig. 1. PGE levels in placental tissue from 20 control patients and 22 patients with pre-eclampsia. Results are expressed as picograms per milligram of wet tissue weight. The solid line across the data points indicates the mean value. Standard deviations are listed at the bottom of the figure.

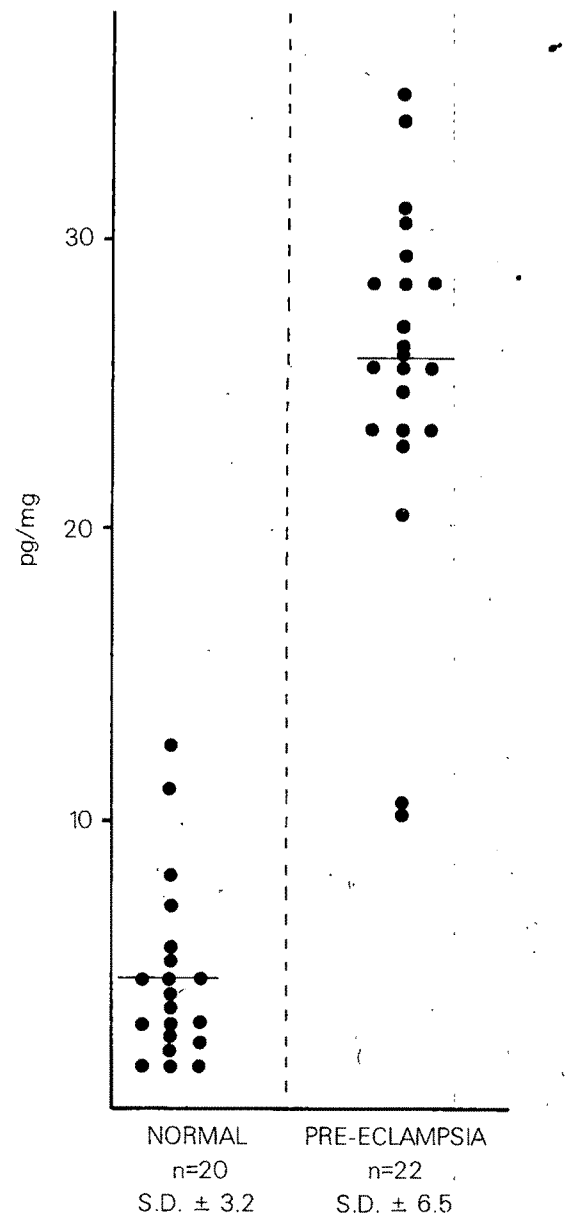


Fig. 2. PGF levels in placental tissue taken from 20 control subjects and 22 patients with pre-eclampsia. Results are expressed as picograms per milligram of wet tissue weight.

pre-eclamptic women revealed no previous history of hypertension, renal disease, or diabetes mellitus.

Newborn weight, gestational age, Apgar scores at one and five minutes, and placental weight were recorded for both normal and pre-eclamptic patients. Prostaglandin (PG) radioimmunoassays were performed with the use of antiserum prepared in rabbits against the albumin conjugate of $PGF_{2\alpha}$ and PGE_1.

The PGF antiserum used in these studies had 100 per cent cross-reactivity with $PGF_{2\alpha}$, 42 per cent cross-reactivity with $PGF_{1\alpha}$, and less than 1 per cent cross-reactivity with PG's of the E, A, and B series as well as the 13,14 dihydro, 15 keto $F_{2\alpha}$. Cross-reactivity studies with the PGE antiserum indicated 100 per cent cross-reaction with PGE_1, 70 per cent cross-reactivity with PGE_2, 88 per cent reactivity with PGA_1, 51 per cent reactivity with PGA_2, 14 per cent reactivity with PGB_1, 6 per cent reactivity with $PGF_{2\alpha}$, and less than one per

cent cross-reactivity with other related PG compounds including the 13,14-dihydro, 15-keto PGE metabolite.

Placental tissue was thawed and extracted initially with ethyl acetate : isopropanol : 0.1M hydrochloric acid (3 : 3 : 1). Following a saline wash step, the ethyl acetate layer containing the PG's was removed and applied to a Silicic acid column for chromatographic separation of the individual PG series. PGE was eluted from the column with a 60:40:2 benzene–ethyl acetate–methanol solvent front, while PG's of the F series were eluted with a 60:40:20 benzene–ethyl acetate–methanol solvent front. The elutions were evaporated and reconstituted with 1 ml. of ethanol in preparation for the radioimmunoassay. Radioimmunoassay was performed as previously described with results expressed as picograms per milligram of wet tissue weight.[3]

Data were analyzed statistically by analysis of variance. Significance between two groups was determined by the method of least significant differences. A P value of 0.05 or less was considered to be significant.

Results

PGE levels were markedly decreased ($P < 0.05$) in pre-eclamptic placental tissue, as shown in Fig. 1. In contrast, PGF concentrations were significantly elevated ($P < 0.05$). (Fig. 2). PG levels did not correlate with the severity of the pre-eclampsia.

Comment

Uteroplacental ischemia observed in pre-eclampsia could be due to an alteration in PG metabolism. Speroff has proposed that the development of pre-eclampsia may represent defective PG production, loss of response to PG, or a combination of these abnormalities.[1]

Placental levels of PGF were found to be significantly increased in pre-eclampsia. These compounds are well-known vasoconstrictors and may reduce uteroplacental blood flow in human subjects.[2] In the fetal lamb, $PGF_{2\alpha}$ increases arterial pressure, umbilical blood flow, and umbilical vascular resistance.[4]

Our studies have also demonstrated diminished levels of PGE in the placenta of a pre-eclamptic patient. The effect of PGE's on the placental vasculature is unclear, although, in general, these agents are potent vasodepressors.[1] Ryan and his co-workers[5] isolated a compound from the human placenta with the biological and chemical properties of PGE. They reported reduced levels of this material in placentas from four pre-eclamptic women. In 1938, von-Euler found that a crude prostaglandin preparation, probably containing both PGF and PGE, produced vasoconstriction in human placental vessels. Recently, Novy and his associates[4] observed marked vasoconstriction in the placental bed of fetal lambs after PGE_2 injection. An initial decrease in fetal arterial pressure was seen. Alam and colleagues[6, 7] reported impaired PGE_1 metabolism in supernatant preparations from placentas of pre-eclamptic patients and have recently found similar metabolic changes in patients with hydatidiform mole. They propose that a reduction in the conversion of PGE_1 to PGA could lead to hypertension.

Our observations support the proposal that prostaglandin synthesis and/or metabolism is altered in pre-eclampsia. Whether this abnormality is a primary event or develops secondary to changes in other regulatory mechanisms demands further study.

REFERENCES

1. Speroff, L: Toxemia of pregnancy, Am. J. Cardiol. **32:** 582, 1972.
2. Pulkkinen, M. O., Pitkanen, Y., Ojala, A., and Hannelin, H.: Decrease of uteroplacental blood flow during prostaglandin $F_{2\alpha}$ induced abortion, Prostaglandins **9:** 61, 1975.
3. Demers, L. M., Yoshinaga, K., and Greep, R. O.: Prostaglandin F in uterine fluid during the menstrual cycle and following steroid treatment, Prostaglandins **5:** 513, 1974.
4. Novy. M. J., Piasecki, G., and Jackson, B. T.: Effect of prostaglandins E_2 and $F_{2\alpha}$ on umbilical blood flow and fetal hemodynamics, Prostaglandins **5:** 543, 1974.
5. Ryan, W. L., Coronel, D. M., and Johnson, R. J.: A vasodepressor substance of the human placenta, Am. J. Obstet. Gynecol. **105:** 1201, 1969.
6. Alam, N. A., Clary, P., and Russell, P. T.: Depressed placental prostaglandin E_1 metabolism in toxemia of pregnancy, Prostaglandins **4:** 363, 1973.
7. Alam, N. A., Clary, P., Shade, A. R., and Russell, P. T.: Absence of prostaglandin E_1 metabolism in hydatidiform mole, Am. J. Obstet. Gynecol. **119:** 1131, 1974.

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

A new operation for uterine displacements

JAMES ALEXANDER ADAMS
Glasgow Medical Journal, vol. 17, pp. 437-446, 1882

made obliquely, and directed towards the mesial line, and this oblique direction will be found to facilitate the search for the ligamentous fibres much better than a vertical opening. The search for the fibres of the ligament must be made cautiously, and with much patience and little haste, for this is the difficult part of the operation. When fairly exposed, clearly traced, and isolated, they should be grasped by broad-pointed forceps—small polypus forceps are very suitable—and, following the guidance of the ligament, the forceps should be thrust well into the inguinal ring, and the ligament laid hold of as high up as possible. When it begins to yield to the traction, it may be pulled out to any desirable extent. Five or six catgut ligatures, passed over and under the ligament, will sufficiently ensure its attachment to the surrounding tissues, while separate ligatures close the wound, excepting at the most dependent part. Antiseptic dressing, strict rest in bed, and the action of the bowels restrained for a few days by means of opiates, should suffice for the after treatment.

Unless after some previous practice on the dead subject, there will be much risk of failure in fairly recognising and in fully grasping the round ligament. In some subjects the fibres are so small and friable that they will bear little traction of the portion first exposed. It would then be necessary and quite justifiable—and for this recommendation I have Professor Cleland's approval—to grasp *all* the structures lying within the inguinal ring. When this is done, and a little care exercised, the body of the ligament may be secured and brought down in nearly every case.

When the ligaments are drawn out and fastened to the pubes in the dead subject, and the uterus examined *in situ* from the open abdomen, the organ is found to occupy an erect and perfectly normal position in the pelvis, and it is only when excessive traction is made that the uterus is drawn close to the pubes. But even in such conditions it is easily demonstrated that the bladder would not be hindered in its function, for it rises *pari passu* with the uterus, and when filled with water it distends readily, and mounts upward behind the pubes.

There are conditions which may render an operation unsuitable. Of these the most obvious are the presence of large heavy tumours connected with the uterus, or the existence of adhesions of that organ to the neighbouring viscera, caused by inflammatory action at some previous part of the patient's history. A careful examination under chloroform is therefore a prudent preliminary before deciding on the operation, and it

Retroversion of the uterus and its treatment with various pessaries and suspension operations attracted considerable interest during the latter part of the nineteenth and early twentieth centuries. In 1882, both Adams, of Glasgow, and William Alexander, of Liverpool (Med. Times Gazette 1: 327, 1882) described uterine suspension by shortening the round ligaments and plicating them in the inguinal canal. Adams carefully developed the procedure by dissection on cadavers. His technique entailed, ". . . an incision made over the external inguinal ring, and a very careful disection carried downwards, expose the pale and straggling fibers of the round ligament as they emerge from the ring . . . these fibers are grasped by the forceps *en masse*, . . . (and) draw them freely outwards to the extent of one or more inches . . . . The incision, about two inches in length, should be . . ." (continued in the illustration). The Alexander-Adams uterine suspension was carried out not only for retrodisplacements but also for uterine prolapse and was widely practiced for several decades.

CURRENT DEVELOPMENTS

Oral contraceptive–induced hypertension—Nine years later

JOHN H. LARAGH, M.D.

New York, New York

Nine years have gone by since oral contraceptive hypertension was first recognized as a clinical entity. In that time it has become apparent that what at first was thought to be a rare disorder is extremely common. Indeed, overt hypertension develops, in time, in about 5 per cent of Pill users. Increases in blood pressure, albeit within the normal range, are still more common. Pill hypertension may develop gradually. It is sometimes quite severe, and it is characteristically reversible within a few months after therapy is stopped. Oral contraceptives produce changes in the renin-angiotensin-aldosterone system, particularly a consistent marked increase in the plasma renin substrate concentration which may be associated with increases in plasma renin activity and aldosterone excretion. The estrogenic component of contraceptive pills appears to be the more important factor in producing abnormalities in the renin system. The mechanisms for the hypertensive response are not entirely clear since normotensive women using the pill may exhibit similar or even more marked changes in the renin axis. The pressor response could have both volume *and* vasoconstrictor *components mediated by the sodium-retaining effects of the estrogen in the presence of a relatively, if not an absolutely, higher plasma renin activity, with the latter being held abnormal by the high plasma renin-substrate levels. A failure of the kidneys to fully suppress renal renin secretion could thus be an important predisposing factor. Our in vitro experiments support the idea that the increased substrate is involved in pathogenesis because they indicate that in normal subjects plasma renin substrate is not present in "excess." Thus, a doubling of the physiologic levels of substrate by oral contraceptives leads to an almost twofold increase in the capacity for angiotensin production as indicated by studies of the initial reaction velocity. These observations define certain guidelines for applying oral contraceptive therapy. At least one base-line blood pressure measurement should be obtained, and blood pressure and weight should be followed at two- or three-month intervals during treatment. Furthermore, oral contraceptive therapy may be contraindicated in women with a history of hypertension, renal disease, toxemia, or fluid retention. Others in whom oral contraceptives are relatively contraindicated include those with a positive family history of hypertension, younger women in whom a longer term commitment is likely, and groups, such as blacks, especially prone to hypertensive phenomena.*

From the Hypertension Center and Cardiovascular Center, The New York Hospital–Cornell Medical Center.

Reprint requests: Dr. John H. Laragh, Hypertension Center and Cardiovascular Center, The New York Hospital–Cornell Medical Center, 525, E. 68th St., New York, New York 10021.

IT HAS BEEN ABOUT nine years now since my associates and I[1] reported an association between oral contraceptives and hypertension. In the same year, Woods[2] independently reported on similar clinical observations. In our study the blood pressure of 11

hypertensive women dropped markedly, in some instances to normal, when the oral contrceptive pill was discontinued. Two of the women, challenged with another oral contraceptive, again became hypertensive. Since then, our findings have been confirmed many times here and abroad and in studies with far larger samples than ours.[3–9] Harris[10] has reported that reversal of malignant hypertension occurs after oral contraceptives are withdrawn. Strokes have also been associated with the oral contraceptive pill[11, 12] but without a clear involvement of hypertension. Moreover, the large-scale studies conducted at the Kaiser-Permanente Medical Center[13] and at the Royal College of General Practitioners[14] suggest that development of hypertension is related to the duration of medication; indeed, the California study reported systolic pressure rises in *all* women after three years of oral contraceptive use.

The reported incidences of hypertension caused by oral contraceptive use range from just a few per cent[7, 8] up to 18 per cent or more.[3, 5, 6, 9] The higher figures cause one to question diagnosis, which doubtless reflects small blood pressure increases within the normal range. By conservative standards, it now appears fairly reasonable to state that about 5 per cent of women using oral contraceptives develop overt hypertension.[13, 14] This is a far greater incidence than my associates and I[1] imagined at the time of our original report. The consequences are said to run the gamut of hypertensive phenomena—from mild manifestations resembling essential hypertension to malignant hypertension, the occurrence of stroke, and even renal failure.[15]

A twentieth of the many millions of women using the oral contraceptive pill is a large number of women with induced hypertension (about a half million in the United States), and it provides good reason for concern. Some concern must also be summoned in behalf of the even larger group of women in whom an oral contraceptive–induced rise in blood pressure seems to occur within "normal" confines; the finding affects the scales of the risks-benefits equation when it is considered that actuarial studies suggest that the blood pressure most clearly favoring longevity and low morbidity is the very lowest compatible with proper circulatory function. The possible impact of a five- to ten-year period of a woman's life in which the blood pressure is even slightly elevated over its natural base line is to be worried about, even without hard data. A number of investigators have reported the clinical impression that the oral contraceptive seems to potentiate a latent tendency for hypertension which in the absence of the oral contraceptive might express itself later. If so, these vulnerable women are being exposed to a longer duration of hypertension than prior physiopathology had in store for them.

Notwithstanding these considerations, few, if any, suggest the abandonment of oral contraception except in the clear indications I will discuss later. The advantages of family planning by this means and the short-view preferences of human nature are such that most women would probably accept an even greater risk to avoid an unwanted pregnancy. Surely not to be discounted on the other side of the scales, too, are the risks of pregnancy itself including hypertension and toxemia.

The last association properly raises the intriguing question of pathophysiology, the answer to which may provide the best way out of the dilemma. The original finding of my associates and I,[1] in 1967, occasioned some surprise, but hindsight reminds us that it need not have. After all, hypertension is the most common complication of natural pregnancy, so it might have been suspected *a priori* that the mimicry of pregnancy induced by gonadal hormones could be associated with some of the same physiologic problems. A search into the reasons for the association leads us into mechanisms shared by a number of other causes of hypertension and may help enlarge our understanding of the larger clinical problem, its diagnosis, and its treatment.

A logical starting point is to examine the effects of oral contraceptives on what we have come to believe holds the keys to blood pressure control: the renin-angiotensin-aldosterone (RAA) system.[16]

The RAA system and its response to oral contraceptives

The RAA system is a complex of hormones and enzymes linked in a sequence of biochemical transactions between the kidney and the adrenal cortex.[16] Its apparent interactions are illustrated in Fig. 1. Whenever a fall in arterial pressure and renal perfusion is induced by any of various stimuli that might reduce "effective" blood volume, such as hemorrhage, sodium depletion, posture, or a transudation situation (i.e., edematous states), the kidney secretes renin into the bloodstream. Renin acts enzymatically on a plasma globulin to release angiotensin I, which is then rapidly hydrolyzed to angiotensin II by pulmonary and plasma converting enzymes. Angiotensin II, in addition to its potent and immediate arteriolar vasoconstricting action, stimulates aldosterone secretion by the adrenal cortices. Aldosterone then acts on the kidney to cause sodium retention. The positive sodium balance brings about retention of water, expansion of the extracellular fluids, and increased filling of the arterial tree. Thus,

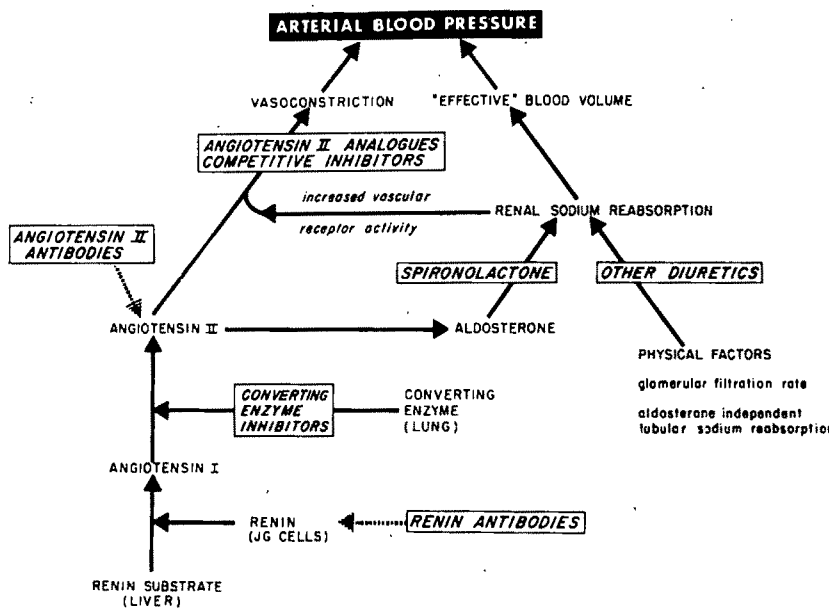


Fig. 1. The RAA system and the cybernetics of sodium and volume homeostasis is shown. The vasoconstriction-volume hypothesis for control of blood pressure is presented.

angiotensin II and aldosterone together raise arterial pressure and restore renal perfusion. The latter effect compensates the system by shutting off the initial signal for renal renin release.

The final mechanism for triggering renin release is not identified, but it appears to involve pressure- or stretch-sensitive receptors in the renal afferent arterioles, a distal tubular macula densa cell receptor responsive to changes in sodium delivery, changes in autonomic nerve and beta-receptor activity, and changes in plasma potassium levels. Increases in plasma angiotensin levels can also "feed back" to retard further renin secretion.

In deciding to study the effect of oral contraceptives on the RAA system, my colleagues and I[16] were prompted by our previous work suggesting that this system was implicated in other forms of hypertensive disease.[16, 17] In addition, Helmer and Judson[18] had shown that estrogen administration may be associated not only with fluid retention but also with increased levels of renin substrate. A further connection was suggested by the demonstration of increased aldosterone secretion after administration of estrogen.[19, 20]

Among the susceptible women we studied, the typical pattern after administration of oral contraceptives (even readministration after withdrawal and the recovery of normal blood pressure) was a marked increase in blood pressure accompanied by a rise as marked in plasma renin substrate and lesser increases in renin and aldosterone activity. Then, with the appearance of hypertension, plasma renin content and "activity" both tended to fall back to normal, even as the plasma renin substrate levels continued to rise.

Fig. 2 shows the time course of recovery for four women who had developed a blood pressure increase while using oral contraceptives.[17] Note that renin substrate levels may remain elevated for as long as four weeks, and it may take as long as 12 weeks or more for blood pressure levels to subside after withdrawal of the oral contraceptive pill. However, plasma renin activity fell to normal or subnormal within four weeks. Similar findings have been made in a number of other centers,[18–20] confirming the consistent rise in blood pressure and in renin substrate levels often lasting long after discontinuation of the oral contraceptive pill but with an associated inconsistent behavior of plasma renin "activity."

These observations are not overly helpful in supporting the hypothesis of oral contraceptive–induced hypertension which postulates that renin activity (the determinant of the production of the pressor, angiotensin II) is central to the problem. While plasma renin activity was high in some of those patients exhibiting hypertension, it was normal or even low in others; in those in whom it became high initially, it tended to fall after overt hypertension had been established. Even more confounding is the finding that similar abnormal hormone patterns have been observed in almost all women using the oral contraceptive pill without the development of hypertension.[6, 19, 20] In

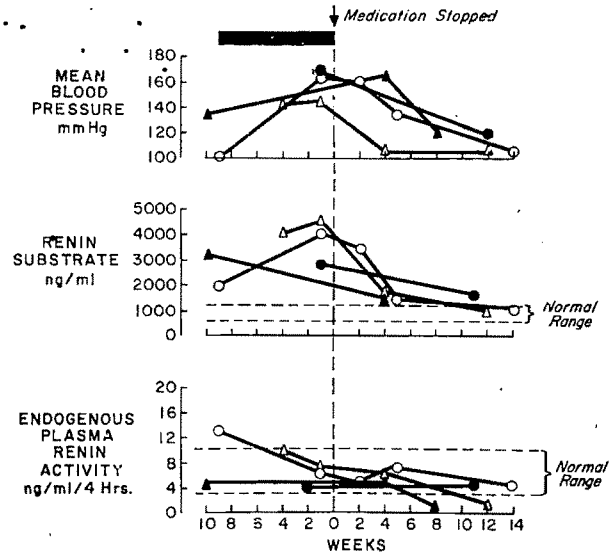


Fig. 2. Effects of withdrawal of oral contraceptives in four patients. After withdrawal of medication, elevated blood pressure was improved in two and completely corrected in two others. At the same time, elevated plasma renin levels returned to normal and plasma renin levels, though not abnormal, tended to decline. It should be noted that plasma renin concentration levels were at times elevated earlier in treatment but tended to decline as therapy was continued. (From Newton and associates.[17])

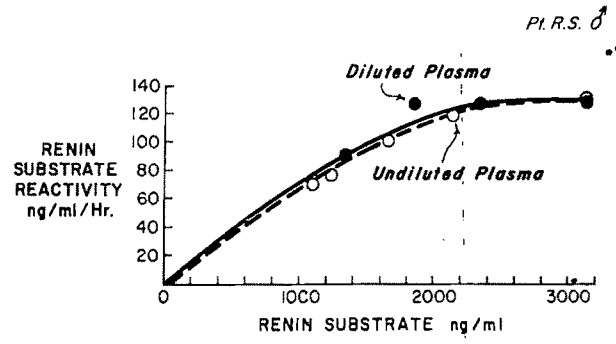


Fig. 3. Effect of dilution of renin substrate on the rate of generation of angiotensin compared with undiluted samples of various concentrations. These samples were obtained at different times in the course of oral contraceptive administration. Since plasma renin concentration is normally about 1,000 ng. per milliliter when measured by this bioassay method, it is apparent that increases in substrate above the normal can markedly increase the capacity to release antiotensin and are probably related to changes in the plasma renin concentration rather than a variation in concentration of an activator or inhibitor. The substrate reactivity as plotted on the ordinate represents the initial reaction velocity and is derived from studies of less than 20 per cent substrate utilization. In these studies the concentration of renin added was 0.85×10^{-3} Goldblatt units per milliliter. (Data printed are from Newton and associates.[17]) The "true" renin substrate values in man as now determined by radioimmunoassay are about twice as high as those shown here.

fact, in some of these normotensive women, plasma renin activity rose well beyond that observed in hypertensive women. Indeed, one report has claimed that plasma angiotensin II values in normotensive women using the oral contraceptive pill were similar to those observed in patients with malignant hypertension.[20]

Accordingly, our current impression, much in need of verification by matched controls, is that plasma renin activity may rise more consistently in normotensive women using the oral contraceptive pill than in those who develop hypertension. If this turns out to be correct, it would fortify the view that oral contraceptive–induced hypertension, as all hypertension, is another pathophysiologic entity fitting into a family of disorders involving abnormal vasoconstriction-volume interplay.[21] Thus, oral contraceptive–induced hypertension may resemble mineralocorticoid hypertension in which plasma renin activity becomes absolutely or *relatively* suppressed, perhaps as a consequence of abnormal sodium retention and increased volume, with the resultant high blood pressure itself working on the renal macula densa and baroreceptors. In other expressions, a substrate-induced absolute or *relative* excess of plasma renin activity relative to the induced state of volume expansion[21] may be the final determinant of the elevated blood pressure caused by the oral contraceptive pill (Fig. 1).

However, while increased renin activity is inconsistent in the hypertensive women using the oral contraceptive pill, renin substrate is definitely not; indeed, a marked increase in plasma renin substrate is the most consistent consequence of oral contraceptive use in all women.[1, 16, 18] The next question is: How would this affect blood pressure in view of a generally held belief that a relative excess of renin substrate is *already* present in normal man and that the rate of angiotensin generation thus depends on the supply of renin?

The answer to the question may be that some aspects of that long-standing belief may need changing, at least with respect to what constitues a "relative excess." To study this, we conducted in vitro experiments in which we added a constant amount of highly purified renin to the serum of patients with oral contraceptive–induced increases in substrate levels.[17] We found that the capacity to generate angiotensin II increased linearly with increases in substrate levels (Fig. 3), and the response did not fall off until substrate values rose two or more times that of normal. Other studies have confirmed this.[9, 19]

Why, then, does not oral contraceptive–induced sub-

strate increase bring about increased angiotensin production with consequent hypertension in *all* patients in whom the substrate increase can be shown, which is to say virtually most women using the oral contraceptive pill? It is compelling to speculate that the normotensive patients can compensate for the excess substrate by an autoregulation that fully suppresses renin secretion. Thus, the hypertensive woman might be defined as one whose compensatory mechanisms for renin secretion are absent, insufficiently thorough, or set to yield inappropriately large responses to various physiologic stimuli.[16] The crack in this logic is that it suggests that renin levels in the normotensive woman, whose buffer mechanisms are presumed intact, should be considerably *less*, on the average, than in those with hypertension. As indicated already, this is not always the case. Indeed, renin values in some hypertensive oral contraceptive users may be lower than in normotensive ones.[6, 18–20, 22]

A possible plug for the crack is the role of factors other than angiotensin in some cases of oral contraceptive–induced hypertension, i.e., the effect of the volume component of the hypertension on the suppression of renin secretion. A candidate for this role is estrogen itself; its sodium-retaining property induces a hydremic effect[2, 3] akin to that of aldosterone excess. Estrogen has been noted in experimental animals[24] to have unique renal tubular effects in addition to the adrenal mineralocorticoid effect. Increased blood volume and cardiac output are more common clinical observations in women using the oral contraceptive pill,[20] as in pregnant women, in whom estrogen and progestogen activity is heightened. It then would appear likely that in oral contraceptive–induced hypertension the volume factor in hypertensive phenomena may be the more predominant.

But the vasoconstrictive factor cannot be discounted. It is also possible that in addition to the activating effect of stimulating substrate levels estrogen may directly stimulate renal renin secretion and so counterbalance renin-suppressing compensatory mechanisms.[16] Thus, in some patients using the oral contraceptive pill we observed increases in renin activity beyond what could be explained by the increased substrate.

An examination of the role of gonadal hormones in oral contraceptive–induced hypertension invites comparison with other hypertensive states in which either natural or therapeutic excess of these substances exists. Hypertension is the most frequent complication of pregnancy, a state which is also associated with heightened estrogen and progestogen activity as well as with consistent increases in plasma renin concentration[25] or activity.[26, 27] Marked increases in aldosterone secretion have been described in the third trimester of normal pregnancy.[28, 29] However, there is only fragmentary information concerning these renal-adrenal hormones in toxemia of pregnancy. The evidence available suggests that aldosterone[28, 29] and renin levels[26, 30] may become normal or even subnormal when this hypertensive condition develops. Accordingly, it is difficult to implicate the RAA system, except in a secondary or reactive way. Furthermore, as both estrogen and progesterone are increased in normal pregnancy, it is difficult to know which, if either, might be involved in the development of toxemia.

It is also known that the pregnant uterus is normally rich in renin content, but the role of this uterine renin in either normal pregnancy or toxemia has not yet been determined.[31, 32] Present evidence suggests that uterine renin does not contribute to plasma levels.

Two other clinical situations reinforce the idea that estrogen treatment alone can have pressor consequences. One involves hormonal management of prostatic cancer, and it is another illustration of delay in recognizing the pressor effect of estrogen administration. Only after some 40 years was it realized that the modest reduction in deaths from this form of cancer with estrogen therapy was counterbalanced by a rise in deaths from other causes in the treated group, primarily heart disease and stroke, with sodium retention a likely culprit.[33] The RAA system has not been studied systematically in this condition.

In the menopausal syndrome, too, long-term estrogen therapy has been widely applied for decades, yet only very recently has a report[5] appeared which associates the use of conjugated estrogens with the development of hypertension. In four of the five cases reported, hypertension disappeared after cessation of treatment. Further substantiation is required.

That estrogen may be the principal oral contraceptive component responsible for RAA system changes is supported by studies in male volunteers on our research ward.[17] The study showed that the administration of norethynodrel, a synthetic steroid with largely, but not exclusively, progestogenic activity, produced significant but small increases in renin substrate levels with corresponding associated increases in plasma renin activity. Ethinyl estradiol produced similar but quantitatively more striking effects. These data suggest that the estrogenic component is the major causative factor in the observed changes in the RAA system.

Crane and associates[34] and Katz and Beck[35] have obtained similar results in more recent studies. Another study in the rat indicates that the elevations of renin substrate levels can occur within several hours after intravenous administration of estrogen.[36] How-

ever, while progestogens may not be a factor in the renin substrate stimulation, this does not exclude the possibility that they participate in other ways in pressor reactions.[37-39]

Clinical implications

Until we know enough to come up with a biochemical solution to the risks of oral contraceptives, either a safer and better adaptation of the present principle or one based on entirely different physiologic principles, we remain fairly well committed by social and medical preference to the continuation of oral contraceptives as the major instrument of family planning. However, we do know enough now to be much more careful in their use.

It would be helpful if we could identify the susceptible woman in advance, but the data so far provide only suggestions and virtually no hard indications. Nevertheless, the prudent physician deals with likelihoods in the absence of certainties every day, and we cannot well ignore the suggestions for the rather long period of time it will take for prospective studies to confirm or disprove them. Caution compels either the contraindication of oral contraceptives or their use with the greatest care in women with a history of hypertension, pre-existing renal disease, a history of toxemia or hypertension during pregnancy, a familial tendency to hypertension and its consequences, or a history of excessive weight gain or fluid retention during the menstrual cycle. Some other groups in whom oral contraceptives are contraindicated may include younger women in whom a longer term commitment is likely and members of ethnic groups such as blacks who are especially susceptible to hypertension.

The absolute designation of the vulnerable woman is, of course, empiric, and this aspect cues the thorough monitoring of all women using the oral contraceptive pill, with even greater rigorousness in the case of the woman for whom social or medical necessity may weigh taking a chance against the above-suggested contraindications. Weight gain, one of the surest and earliest indications of sodium and water retention, should be reported immediately by the patient. Any woman using the oral contraceptive pill should have a blood pressure determination at least once before starting therapy and no later than two months after therapy is started; blood pressure should be checked frequently thereafter and compared with the adequately established base line.

The pharmacologic challenge is to make a better oral contraceptive pill. We do not yet know if all varieties now on the market have equal potential for inducing hypertension or if altering the proportion of estrogen and progestogen in favor of the latter would have a beneficial effect. We need to study this. It might also be possible to design a prescription for the susceptible woman to include the compensation she lacks—perhaps a spirolactone-improved pill for even greater aldosterone antagonism or, even better, an agent like propranolol, now known to block renin secretion[16, 40] and thus also to curtail aldosterone secretion and retention of fluid. Such approaches would attack the hypertension at its source in the RAA system or, quite properly, permit the specific containment of either the *volume* or the *vasoconstriction* factors controlled by the system.[21] If this can be worked out, it may prove a more direct and physiologic correction than the current a posteriori repair of hydremia, which is to pump the patient dry with diuretics.

REFERENCES

1. Laragh, J. H., Sealey, J. E., Ledingham, J. G., et al.: Oral contraceptives. Renin, aldosterone, and high blood pressure, J. A. M. A. **201:** 918, 1967.
2. Woods, J. W.: Oral contraceptives and hypertension, Lancet **2:** 653, 1967.
3. Tyson, J. E.: Oral contraception and elevated blood pressure, Am. J. Obstet. Gynecol. **100:** 875, 1968.
4. Weinberger, M. H., Collins, R. D., Dowdy, A. J., et al.: Hypertension induced by oral contraceptives containing estrogen and gestagen. Effects on plasma renin activity and aldosterone excretion, Ann. Intern. Med. **71:** 891, 1969.
5. Crane, M. G., Harris, J. J., and Winsor, W., III: Hypertension, oral contraceptive agents, and conjugated estrogens, Ann. Intern. Med. **74:** 13, 1971.
6. Sarutta, T., Saade, G. N., and Kaplan, N. M.: A possible mechanism for hypertension induced by oral contraceptives. Diminished feedback suppression of renal disease, Arch. Intern. Med. **126:** 621, 1970.
7. Goodlin, R. C., and Waechter, V.: Oral contraceptives and blood pressure, Lancet **1:** 1262, 1969.
8. Kunin, C. M., McCormack, R. C., and Abernathy, J. R.: Oral contraceptives and blood pressure, Arch. Intern. Med. **123:** 362, 1969.
9. Weir, R. J., et al.: Blood pressure in women taking oral contraceptives, Br. Med. J. **10:** 535, 1974.
10. Harris, P. W.: Malignant hypertension associated with oral contraceptives, Lancet **2:** 466, 1969.
11. Cole, M.: Strokes in young women using oral contraceptives, Arch. Intern. Med. **120:** 551, 1967.
12. Oral contraceptives and stroke in young women. Associated risk factors. Collaborative group for the study of stroke in young women, J. A. M. A. **231:** 718, 1975.
13. Ramcharan, S., Pellagrin, F. A., and Hoag, E.: The occurrence and course of hypertensive disease in users and nonusers of oral contraceptive drugs, *in* Fregley, M. J., and Fregley, M. S., editors: Oral Contraceptives and High Blood Pressure, Gainesville, Florida, 1974, The Dolphin Press, pp. 1-16.
14. Oral contraceptives and health: An interim report from the oral contraception study of the Royal College of General Practitioners, London, 1974, Pitman Medical.
15. Zacherle, B. J., and Richardson, J. A.: Irreversible renal

failure secondary to hypertension induced by oral contraceptives, Ann. Intern. Med. **77:** 83, 1972.
16. Laragh, J. H., Baer, L., Brunner, H. R., Bühler, F. R., Sealey, J. E., and Vaughan, E. D., Jr.: Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease, Am. J. Med. **52:** 633, 1972.
17. Newton, M. A., Sealey, J. E., Ledingham, J. G., et al.: High blood pressure and oral contraceptives. Changes in plasma renin and renin substrate and in aldosterone excretion, AM. J. OBSTET. GYNECOL. **101:** 1037, 1968.
18. Helmer, O. M., and Judson, W. E.: Influence of high renin substrate levels on renin-angiotensin system in pregnancy, AM. J. OBSTET. GYNECOL. **99:** 9, 1967.
19. Skinner, S. L., Lumbers, E. R., and Symonds E. M.: Alteration by oral contraceptives of normal menstrual changes in plasma renin activity, concentration and substrate, Clin. Sci. **36:** 67, 1969.
20. Cain, M. D., Walters, W. A., and Catt, K. J.: Effects of oral contraceptive therapy on the renin-angiotensin system, J. Clin. Endocrinol. Metab. **33:** 671, 1971.
21. Laragh, J. H.: Vasconstriction-volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles, Am. J. Med. **55:** 261, 1973.
22. Beckerhoff, R., Luetscher, J. H., Wilkinson, R., et al.: Plasma renin concentration activity, and substrate in hypertension induced by oral contraceptives, J. Clin. Endocrinol. Metab. **34:** 1067, 1972.
23. Thorn, G. W., and Harrop, G. A.: The "sodium-retaining effect" of the sex hormones, Science **86:** 40, 1937.
24. Johnson, J. A., Davis, J. O., Baumber, J. S., et al.: Effect of estrogens and progesterone on electrolyte balances in normal dogs, Am. J. Physiol. **219:** 1691, 1970.
25. Brown, J. J., Davies, D. L., Doak, P. B., et al.: Plasma-renin in normal pregnancy, Lancet **2:** 900, 1963.
26. Gordon, R. D., Parsons, S., and Symonds E. M.: A prospective study of plasma-renin activity in normal and toxaemic pregnancy, Lancet **1:** 347, 1969.
27. Robb, C. A., Davis, J. O., Johnson, J. A., et al.: Mechanisms regulating the renal excretion of sodium during pregnancy, J. Clin. Invest. **49:** 871, 1970.
28. Vande Wiele, R. L., Gurpide, E., Kelly W. G., et al.: The secretory rate of progesterone and aldosterone in normal and abnormal late pregnancy, *in* Proceedings of the First International Congress of Endocrinology, 1960, p. 159. (Abst.)
29. Watanabe, M., Meeker, C. I., Gray, M. J., et al.: Secretion rate of aldosterone in normal pregnancy, J. Clin. Invest. **42:** 1619, 1963.
30. Brown, J. J., Davies, D. L., Doak, P. B., et al.: Plasma renin concentration in the hypertensive diseases of pregnancy, J. Obstet. Gynaecol. Br. Commonw. **73:** 410, 1966.
31. Capelli, J. P., Wesson, L. C., Aponte, G. E., Favaldo, C., and Jaffe, E.: Characterization and source of a renin-like enzyme in anephric human, J. Clin. Endocrinol. Metab. **28:** 221, 1968.
32. Ferris, T. F., Gordon, P., and Mulrow, P. J.: Rabbit uterus as a source of renin, Am. J. Physiol. **212:** 698, 1967.
33. Veterans Administration Cooperative Urological Research Group: Treatment and survival of patients with cancer of the prostate, Surg. Gynecol. Obstet. **124:** 1011, 1967.
34. Crane, M. G., and Harris, J. J.: Plasma renin activity and aldosterone excretion rate in normal subject. I. Effects of ethinyl estradiol and medroxyprogesterone acetate, J. Clin. Endocrinol. Metab. **29:** 558, 1969.
35. Katz, F. H., and Beck, P.: Plasma renin activity, renin substrate and aldosterone during treatment with various oral contraceptives, J. Clin. Endocrinol. Metab. **39:** 1001, 1974.
36. Menard, J., Cain, M. D., and Catt, K. J.: Rapid effects of estrogen on the renin-angiotensin system, Clin. Res. **19:** 377, 1971.
37. Brownrigg, G. M.: Toxemia in hormone-induced pseudopregnancy, Can. Med. Assoc. J. **87:** 408, 1962.
38. Horrobin, D. F.: Progesterone and preeclampsia, Lancet **1:** 475, 1968.
39. Douglas, B. H.: Experimental Approaches to Toxemia of Pregnancy, Springfield, Illinois, 1971, Charles C Thomas, Publisher, pp. 1-168.
40. Bühler, F. R., Laragh, J. H., Baer, L., Vaughan, E. D., Jr., and Brunner, H. R.: Propranolol inhibition of renin secretion: A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases, N. Engl. J. Med. **287:** 1209, 1972.

ITEMS

Twenty-first Annual Angus M. McBryde Perinatal Symposium

The Twenty-first Annual Angus M. McBryde Perinatal Symposium (Topics in Perinatal Medicine), sponsored by the Division of Perinatal Medicine, will be held September 15 and 16, 1976, at Duke University Medical Center, Durham, North Carolina. Guest Faculty includes Alfred W. Brann, Jr., M.D., James P. Keating, M.D., and John W. C. Johnson, M.D.

Physician registration fee is $50.00. For information, write to: Angus M. McBryde Perinatal Symposium, Box 3967, Duke University Medical Center, Durham, North Carolina 27710.

Scientific Basis of Current Obstetric and Gynecologic Practice

The Department of Obstetrics and Gynecology of The University of Texas Health Science Center at San Antonio will present the Fourth Annual Postgraduate Course, "Scientific Basis of Current Obstetric and Gynecologic Practice," January 27–February 2, 1977. The course, given in three parts, each under the direction of a distinguished professor, is designed primarily for residents, recent graduates of training programs, and practicing physicians who desire a résumé of basic information and modern clinical practice in obstetrics and gynecology.

Part I: Gynecologic Pathophysiology, directed by J. Donald Woodruff, Professor of Gynecology and Obstetrics and Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Part II: High-Risk Pregnancy, directed by Edward J. Quilligan, Professor and Chairman of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles, California.

Part III: Gynecologic Endocrinology, Genetics, Infertility, and Contraception, directed by Joseph W. Goldzieher, Director of Clinical Sciences and Reproductive Biology, Southwest Foundation for Research and Education, San Antonio, Texas.

The $350 enrollment fee includes a study set of 35 mm. Kodachrome slides, furnished to each registrant for home study. These slides will be reviewed at a seminar immediately after Part I of the course. Registration fee also includes cocktails and dinner on Saturday night, January 29. Saturday afternoon and Sunday, January 30, are free so that registrants may visit places of interest in San Antonio.

The course will be limited to 150 students. Registration must be made by January 1, 1977, and should be accompanied by a check payable to The University of Texas Health Science Center at San Antonio (UTHSCSA). For further details and to register, write to: C. J. Pauerstein, M.D., Department of Obstetrics and Gynecology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

High-Risk Pregnancy

A course on "High-Risk Pregnancy" will be held in the Teaching Center Auditorium at Long Island Jewish–Hillside Medical Center, New Hyde Park, New York, Wednesday, September 15, 1976, 9 A.M. to 5 P.M. It is sponsored by the Department of Obstetrics/Gynecology, Long Island Jewish–Hillside Medical Center and Health Sciences Center, State University of New York at Stony Brook. The course is designed for the practicing obstetrician-gynecologist and family practitioner. Lectures and slide presentations will cover the theory, principles, and practical application upon which current concepts of clinical and laboratory management of "high-risk" pregnancy are based. Registration fee: $25 (includes lunch and coffee breaks).

For further information, contact: Office of the Dean of the Clinical Campus, Long Island Jewish–Hillside Medical Center, New Hyde Park, New York 11040.

Symposium on Nutrition and Cancer

A Symposium on Nutrition and Cancer, sponsored by the Institute of Human Nutrition of Columbia University, College of Physicians and Surgeons, will be held at the Statler Hilton Hotel, Seventh Ave., 32nd to 33rd St., New York, New York, November 18-19, 1976.

The purpose of the meeting is to bring together leading scientists to review the current status of knowledge about the relation of nutrition to cancer. The Symposium will cover the experimental work implicating nutrition as a contributory cause of certain cancers, the epidemiologic evidence suggesting that certain dietary factors may increase cancer risk, and the relation of food additives to cancers, the epidemiologic

evidence suggesting that certain dietary factors may increase cancer risk, and the relation of food additives to cancer. In addition, the weight loss of patients with cancer will be examined from a nutritional standpoint. Finally, both oral and parenteral nutritional therapy in cancer patients will be covered.

For further information write: Director, Institute of Human Nutrition, Columbia University, 511 W. 166th St., New York, New York, 10032.

The National Foundation–March of Dimes

The National Foundation–March of Dimes will entertain a limited number of research proposals for the support of basic and clinical research in birth defects. The National Foundation defines a birth defect as an abnormality of structure, function, or metabolism, whether genetically determined or a result of environmental interference during embryonic or fetal life. Requests dealing with the structure and function of chromosomes, their subunits, genes, supporting structures, repressor substances, and the like will be encouraged. For further information, contact: Vice President for Research, The National Foundation–March of Dimes, 1275 Mamaroneck Ave., White Plains, New York 10605.

Eighth Annual Meeting of the International Family Planning Research Association, Inc.

The Eighth Annual Meeting of the International Family Planning Research Association, Inc., will be held September 29 through October 2, 1976, at the Beverly Hilton, Beverly Hills, California. Registration is open to members and nonmembers of the Association. For further information, contact the Executive Office: Ludwig Lauerhass, Executive Director, 2960 W. 8th St., Los Angeles, California 90005. Telephone: (213) 386-1970.

Data bank of dated events concerning the human menstrual cycle and its interruption

The University of Minnesota and Alan E. Treloar as Principal Investigator announce the establishment of a "data bank" of dated events concerning the human menstrual cycle and its interruption by reason of pregnancy and other causes of amenorrhea. Converted to a file of coded data on magnetic tape, this repository of many thousand person years of menstrual history has already been made available to selected medical scientists. It is now being made available to others having appropriate use for such information in connection with development of their own research programs.

Custody of the original data and their preservation in completely confidential status have been accepted under Deed of Gift by the University of Minnesota on behalf of its Boynton Health Service. A resumé of the program and further information may be secured from the Director at the address below. Copy of the coding protocol presently governing that operation will be provided to those who demonstrate suitable preparedness to enter into collaborative arrangements facilitating research of appealing design. Lyle A. French, Vice President, Health Sciences; Frank B. Wilderson, Jr., Vice President, Student Affairs; Alan E. Treloar, Director, Menstruation and Reproduction Research Program, Boynton Health Service, University of Minnesota, Minneapolis, Minnesota 55455.

Attention: We are trying to locate all nurse-midwives living in or educated in the United States

The American College of Nurse-Midwives will conduct a survey during September and October, 1976, which will provide up-to-date information on nurse-midwives and the practice of nurse-midwifery in the United States and its territories. *If you are (or know) a nurse-midwife* living in the United States or its territories or educated in the United States or its territories (regardless of where you are living now), *we want to include you in this survey.* The information from the survey will not be accurate unless all nurse-midwives, whether or not they are currently working, are included. Please send us your name and address so that we can send you the questionnaire (in September). Everyone who participates in this survey will receive a copy of the final report.

If you are not a nurse-midwife but know of a nurse-midwife who should be included in this survey, please pass this information on to her. Names and addresses of nurse-midwives should be sent to: Judith B. Rooks, C.N.M., M.S., M.P.H., Chairman, American College of Nurse-Midwives Research and Statistics Committee, 356 4th St., N.E., Atlanta, Georgia 30308.

Sixteenth Annual Fall Seminar in Obstetrics and Gynecology of the Shufelt Society

The Sixteenth Annual Fall Seminar in Obstetrics and Gynecology of the Shufelt Society of Santa Clara Valley will be held on Saturday, October 2, 1976, at the LeBaron Hotel in San Jose, California. The topic of this year's Seminar will be, "Endometriosis: Current Principles and Management." The speakers will be Dr. Robert L. Friedlander of Albany Medical College, Dr. Robert B. Greenblatt of the Medical College of Georgia, and Dr. Robert Israel of the University of Southern California. This program is acceptable for seven hours of Group A credit toward the California Medical Association's Certificate in Continuing Medical Education. Further information can be obtained by writing

to: Vincent F. Nola, M.D., Secretary, Shufelt Society, 2081 Forest Ave., San Jose, California 95128.

Fourth Annual Meeting of the Southern Perinatal Association

The Fourth Annual Meeting of the Southern Perinatal Association will be held at the Galatea Inn, Pensacola Beach, Florida, from September 29 through October 3, 1976.

In addition to the business meeting, the program will include three symposiums. The first will be on the "advances of fetal physiology"; the second, on "perinatal infection"; and the third, on "neonatal ventilation." For information, contact: Sister Carol Keehan, R.N., 5151 N. 9th Ave., Pensacola, Florida 32504.

Symposium on Perinatal Medicine

A "Symposium on Perinatal Medicine" will be conducted October 1-3, 1976, at the Memorial Hospital Medical Center of Long Beach–University of California, Irvine, Center for Health Education, 2801 Atlantic Ave., Long Beach, California. The Symposium will consist of a two and a half day program designed to acquaint the practicing obstetrician-gynecologist, pediatrician, and perinatal nurse with modern advances in the care of the high-risk pregnant patient and her newborn infant.

Program directors are Roger K. Freeman, M.D., and Arthur I. Goldstein, M.D. The guest faculty includes Roberta Ballard, M.D., Philip J. DiSaia, M.D., Norman Gant, M.D., John L. Sever, M.D., and Steve Gabbe, M.D.

The program is sponsored by the National Foundation/March of Dimes in cooperation with the Long Beach and Orange County Obstetrics-Gynecology Societies and the Department of Gynecology and Obstetrics, University of California, Irvine. Registration fee is $150.00 for physicians and $75.00 for nurses. This continuing medical education activity is acceptable for credit toward the Physician's Recognition Award of the American Medical Association in Category 1 on a hour-for-hour contact basis.

Further information may be obtained from: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach, California 90801. Telephone: (213) 595-3823.

Course in Pediatric, Adolescent, and Geriatric Gynecology

The Department of Gynecology and Obstetrics of the Albert Einstein College of Medicine announces a course in Pediatric, Adolescent, and Geriatric Gynecology, to be held in Hamilton, Bermuda, October 24 to 30, 1976. Guest faculty includes John I. Brewer of Northwestern University Medical School, Alvin F. Goldfarb of Jefferson Medical College, and Karen Hein of Montefiore Hospital, New York. The course has been approved for 25 cognates by the American College of Obstetricians and Gynecologists and 22 hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association. Inquiries may be directed to the course Director, Irwin H. Kaiser, M.D., Bronx Municipal Hospital Center, Pelham Parkway and Eastchester Rd., Room 709, Bronx, New York 10461, or to the Institute for Continuing Education, P. O. Box 11083, 2405 Westwood Ave., Richmond, Virginia 23230.

What's New in Infectious Disease

A program entitled "What's New in Infectious Disease" will be presented September 10, 1976, at the Children's Hospital, Denver, Colorado, in the Tammen Auditorium, from 12 noon to 4 P.M. For information and registration, please write: MaryAnn Van Gorp, Department of Continuing Education, The Children's Hospital, 1056 E. Nineteenth Ave., Denver, Colorado 80218. Telephone: (303) 861-8888, Ext. 2280.

What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.



ANNOUNCING 7 EFFECTIVE NEW AGENTS FOR THE TREATMENT OF TROUBLESOME CLINICAL ISSUES.

1. THE KIDNEY IN PREGNANCY

Edited by **RUSSELL RAMON de ALVAREZ, M.D.,** Temple University Health Sciences Center

A definitive reference to the current clinical management of pregnant and recently pregnant patients with renal disorders. Authoritative contributors describe the major functions of the kidney required to sustain pregnancy, relevant principles of water and electrolyte physiology, tests of renal function, and the characteristic histology and fine structure of specific pregnancy induced renal disorders as well as other diseases adversely influenced by pregnancy. The clinical course of the problems is discussed and diagnoses and treatments are presented to provide practical guidance for practicing obstetricians, residents, medical students, and other specialists who treat pregnant patients.

1976 224 pages 67 illus. $13.50

2. GYNECOLOGIC ONCOLOGY

By **FELIX RUTLEDGE, M.D.,** M. D. Anderson Hospital and Tumor Institute, **RICHARD C. BORONOW, M.D.,** Gynecologic Tumor Service, University of Mississippi Medical Center, and **J. TAYLOR WHARTON, M.D.,** M. D. Anderson Hospital and Tumor Institute

This is an excellent presentation of this subject which will be of interest to everyone, not only because it presents the experience of the M.D. Anderson Hospital, but because the senior author is a leader in this field of medicine. I do believe this will be an extraordinarily useful text for students and graduates alike, for the experience of these individuals and this institution has been codified in a model fashion. Not everyone with oncologic experience will agree with every method presented, but they will all be respectful of it." S. B. Gusberg, M.D., D.Sc., Professor & Chairman, Department of Obstetrics and Gynecology, Mount Sinai School of Medicine

1976 282 pages 99 illus. $22.50

3. HYPERTENSION IN PREGNANCY

Edited by **MARSHALL D. LINDHEIMER, M.D.,** and **ADRIAN KATZ, M.D.,** both of the University of Chicago Pritzker School of Medicine, and **FREDERICK P. ZUSPAN, M.D.,** Ohio State University

The first integrated survey of knowledge of the hypertensive complications of pregnancy in more than a decade, this volume features the contributions of outstanding authorities in physiology, biochemistry, morphology, obstetrics, medicine, pediatrics, and pathology. Issues discussed include the epidemiology, immunology, and pathology of the kidney and uteroplacental unit; the mechanisms of signs and symptoms such as hypertension, proteinuria, and edema; the normal and disturbed physiology of pregnant humans and animal models; and uterine blood flow, including the effects of antihypertensive agents in animals and human patients.

1976 464 pages 195 illus. $32.00

4. IMMUNOBIOLOGY FOR THE CLINICIAN

By **HUGH R. K. BARBER, M.D.,** Department of Obstetrics and Gynecology, Cornell University Medical College

Here in one readable text are the concepts of immunobiology that are basic to an understanding of the principles and practice of modern medicine. Concise without being superficial, this book provides essential information for obstetricians and gynecologists in daily practice, and an invaluable aid for residents preparing for board examinations. Medical students will appreciate the text's clear, direct, interdisciplinary presentation, and the way each self-contained chapter concludes with a survey of the major points covered and a quick discussion of additional considerations to amplify and explain the information already presented. A convenient glossary and index are included.

Nov. 1976 approx. 350 pages 37 illus. tent. $24.95

5. THE NEONATE: Clinical Biochemistry, Physiology and Pathology

Edited by **DONALD S. YOUNG, Ph.D.,** Clinical Center, N.I.H., and **JOYCELYN M. HICKS, Ph.D.,** Children's Hospital, National Medical Center

A concise, interdisciplinary synopsis of the latest advances in neonatal medicine, with emphasis on the role of the clinical laboratory in the modern care of newborn infants. Background physiology and biochemistry are included to provide the information required for correct interpretation of test data.

1976 350 pages 113 illus. $19.50

6. SYNOPSIS OF GYNECOLOGIC ONCOLOGY

By **PHILIP J. DiSAIA, M.D., C. PAUL MORROW, M.D.,** and **DUANE E. TOWNSEND, M.D.,** all of the Women's Hospital, Los Angeles County/University of Southern California Medical Center

"... a unique, comprehensive treatise on gynecologic oncology...The text is up-to-date with over 700 references...supported by numerous photographs, diagrams, tables and flow sheets....fulfills a great need for background information in a rapidly developing field...it will undoubtedly prove useful for students, residents and fellows in gynecology, and physicians in closely allied fields." *Journal of the American Medical Association,* Oct. 27, 1975

1975 368 pages 149 illus. $19.50

7. EARLY BREAST CANCER: Detection and Treatment

Edited by **H. STEPHEN GALLAGER, M.D.,** the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute

A concise, yet comprehensive review of current clinical management, including thermography, mammography, xeromammography, low dose mammography, specimen radiography, and the team approach to cancer treatment.

Dec. 1975 256 pages 45 illus. $16.50

WILEY MEDICAL

JOHN WILEY & SONS, INC.

605 Third Ave., New York, N.Y. 10016

In Canada: 22 Worcester Rd., Rexdale, Ontario

FREE 10-DAY EXAMINATION OFFER

Place order with your medical book dealer or send this coupon to:

WILEY-MEDICAL

John Wiley & Sons, Inc., Box 513, Somerset, New Jersey 08873

In Canada: 22 Worcester Road, Rexdale, Ontario

(Send check and save postage and shipping charges.)

Please send the books checked at right for a free 10-day examination.* At the end of that time if I am not satisfied I will return the books received and owe nothing.

☐ My check (money order) is enclosed. (Please include applicable sales tax.) ☐ Please bill me.

☐ de Alvarez (1 20030-1)
☐ Lindheimer (1 53783-7)
☐ Barber (1 04785-6)
☐ Rutledge (1 74720-3)
☐ Young (1 97982-1)
☐ DiSaia (1 21590-2)
☐ Gallager (1 29051-0)

Name_____

Address_____

City/State/Zip_____

*Offer valid in U.S. and Canada only. Prices, subject to change without notice, are slightly higher in Canada. Overseas orders, which must be accompanied by

CAMEROUN, AFRICA

Harvard University urgently seeking *OBSTETRICIAN-GYNECOLOGIST with public health interest* for its faculty team at School of Health Sciences, Yaounde, supporting teaching and research in Maternal and Child Health and Family Planning.

Require: Board qualification, ability to use French.

For information, write

Charles A. Janeway, M.D.
300 Longwood Ave. Boston, MA 02115
Tel.: 617-734-6000, ext. 3491

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 1339, Erie, Pennsylvania 16512.

Flagyl®
(metronidazole) 250 mg.

Warning
Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

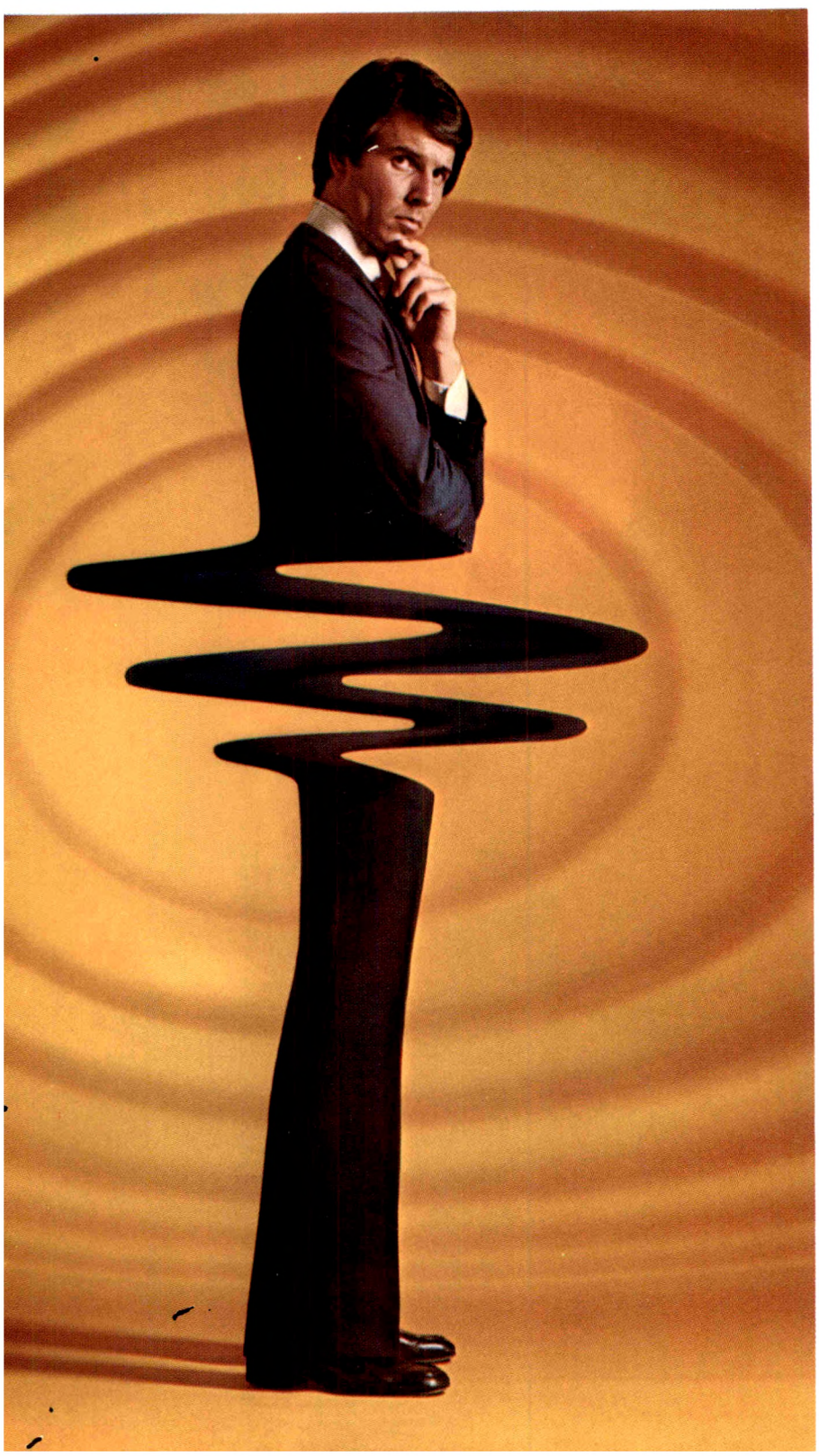
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

SEARLE Searle & Co.
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680.

If men suffered from the symptoms of trichomoniasis, they'd appreciate Flagyl®.

(metronidazole)



Women with trichomoniasis have been grateful for the benefits of Flagyl therapy for over a decade. Most men have no symptoms and are not even aware that they have contracted trichomoniasis, so they rarely appreciate Flagyl. Unless both sexual partners are diagnosed and treated simultaneously, reinfection from the consort is a probability (the "ping-pong" effect).

In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra and the bladder. Only the systemic action of Flagyl can eliminate trichomonads from these sequestered sites.

In the male, only Flagyl can effectively eliminate trichomonads from the male genitourinary tract.

Thus, for the female Flagyl is the treatment of choice. For the male it is the only choice. And that's something they both can appreciate!

Flagyl®
(metronidazole)
250-mg. tablets

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936 •

Please see adjacent page for brief summary of prescribing information.

Happy homecoming for the new mother



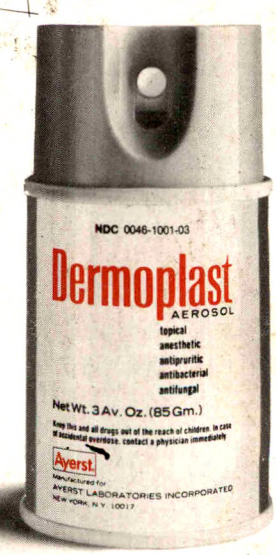
For continued relief of postepisiotomy discomfort, send her home from the hospital with DERMOPLAST® Aerosol

What DERMOPLAST starts doing to relieve postepisiotomy discomfort in the hospital, it can keep doing at home—to help make the new mother's first days with her baby as enjoyable as they should be. DERMOPLAST permeates the suture line without affecting sutures, and relieves itching that accompanies tissue regeneration and hair regrowth.

It will not dry or macerate the skin, and is easily removed with soap and water. DERMOPLAST is easy to apply—sprays from any angle. Available in three sizes, including convenient 3-oz. size that is especially designed for self-administration by the patient.

DERMOPLAST Aerosol Spray contains: Benzocaine, w/w 4.5%; benzethonium chloride, w/w 0.1%; menthol, w/w 0.5%; oxyquinoline benzoate, w/w 1.2%; and methylparaben, w/w 2.0%. Inactive ingredients, vegetable oils and propellant. Also contains 1.9% isopropyl alcohol.

For additional indications, full directions for use, and warnings, see label copy on DERMOPLAST Aerosol Spray can.



Ayerst®

AYERST LABORATORIES
New York, N.Y. 10017

7535

19.2.77

September 15, 1976
volume 126, number 2

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

Official Publication

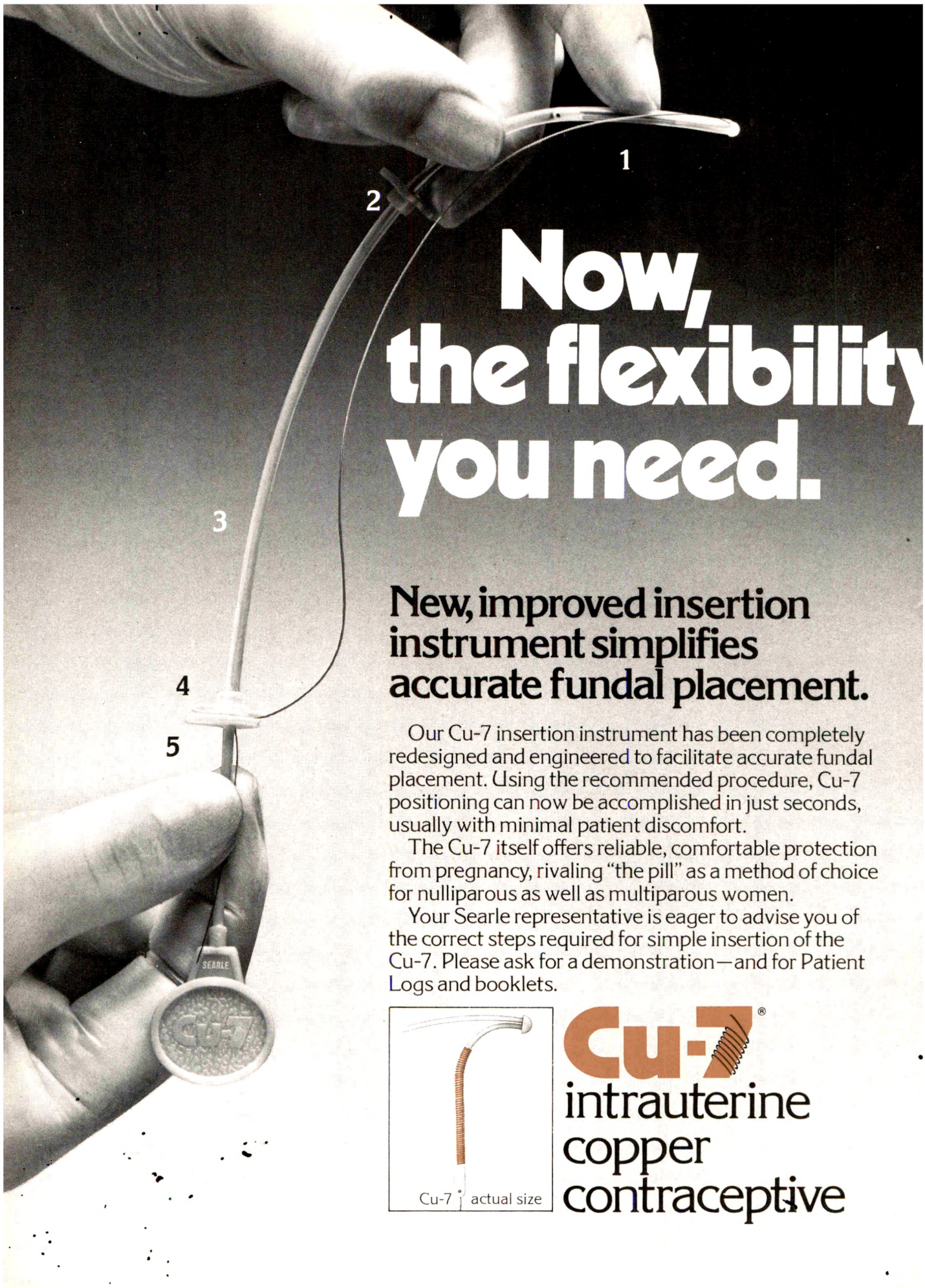
AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY



Published by

THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (2) 151-300 (1976)



Now, the flexibility you need.

New, improved insertion instrument simplifies accurate fundal placement.

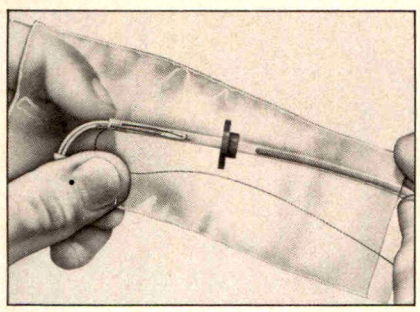
Our Cu-7 insertion instrument has been completely redesigned and engineered to facilitate accurate fundal placement. Using the recommended procedure, Cu-7 positioning can now be accomplished in just seconds, usually with minimal patient discomfort.

The Cu-7 itself offers reliable, comfortable protection from pregnancy, rivaling "the pill" as a method of choice for nulliparous as well as multiparous women.

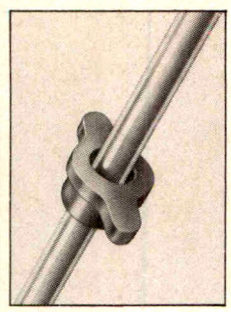
Your Searle representative is eager to advise you of the correct steps required for simple insertion of the Cu-7. Please ask for a demonstration—and for Patient Logs and booklets.

Cu-7®
intrauterine copper contraceptive

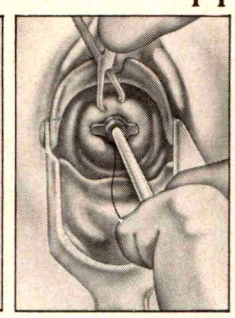
How five newly designed features make it easier to use Cu-7® intrauterine copper contraceptive.



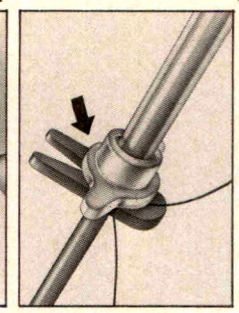
1. New sterile sheath
Helps maintain sterility during loading procedure and cervical-stop setting.



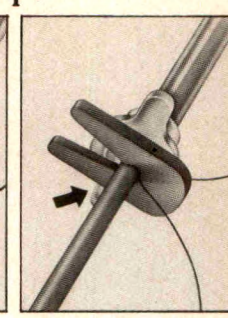
2. New blue-winged cervical stop
A visual guide to aid in correct positioning of the "seven" in the uterus.



3. New flexible rod
Facilitates insertion of "seven" into virtually any normal uterine cavity in seconds.



4. New welded tube-stop
Serves as handle for withdrawing the tube and removal of instrument.



5. New thread-retaining clip
When held to tube-stop during procedure, facilitates insertion and makes tube-crimping virtually impossible.

Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is 89 mg. of pure, virgin electrolytic copper wire providing 200mm^2 of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the copper coil into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication: The Cu-7 is indicated for contraception.

Contraindications: The presence of any of the following, at the time of insertion, constitutes a contraindication: pregnancy, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months, endometrial disease such as hyperplasia or carcinoma and a known or suspected allergy to copper.

Warnings: Recent reports suggest an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. In some cases, initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned of the suggested incidence of increased risk of sepsis and followed with close vigilance.

The long-term effects on the offspring of the presence of copper in the uterus during pregnancy are unknown.

Perforations of the uterus have occurred. In this case the device should be removed immediately.

The use of microwave therapy in patients with metal prosthetics may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients wearing a Cu-7.

Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease, the incidence of which is one in two hundred thousand.

Precautions: A pelvic examination should be done.

Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed shortly following a menstrual period. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed.

Occasional perforations of the uterus (.03%) have been reported, usually during insertion into patients less than two months post abortion or post partum. If penetration into abdominal cavity occurs, laparotomy should be performed and the device recovered. Local inflammatory reaction with abscess formation is a possibility if a device is left in the abdomen.

If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

The Cu-7 should be removed if pelvic infection which is unresponsive to treatment occurs.

The device should be replaced every two years. There is no evidence of decreasing effectiveness with time before two years, but the contraceptive effectiveness of the Cu-7 after two years has yet to be established.

If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to pull on the thread and displace the Cu-7 and told to return in two years for its replacement.

A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman wearing a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being worn.

Adverse Reactions: Perforation of the uterus has occurred.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women.

Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Transient spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. The following complaints have also been reported, although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, and cystitis.

Dosage and Administration: A single Cu-7 is to be inserted into the uterine cavity (see Precautions section). The small diameter of the Cu-7 enables easy insertion into the nulliparous as well as the multiparous uterus. Present information indicates that the efficacy is retained for at least 24 months. Until accurate data indicating a longer effective life become available, the Cu-7 should be removed and a new one inserted on or before 24 months from the date of insertion. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

How Supplied: Available in cartons of 6 and boxes of 30 sterile units (Cu-7 with an inserter) and sufficient patient identification cards.

Clinical Studies: Different event rates have been recorded with the use of different intrauterine contraceptive devices, inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use.) This experience encompasses 321,699 woman-months of use, including 12 months for 9,594 women and 24 months for 7,599.

	12 Months		24 Months	
	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.7	1.3	2.5	2.1
Expulsion	5.5	7.7	6.5	8.7
Medical Removal	9.6	12.7	15.3	18.2
Continuation Rate	78.3	72.9	63.9	59.7

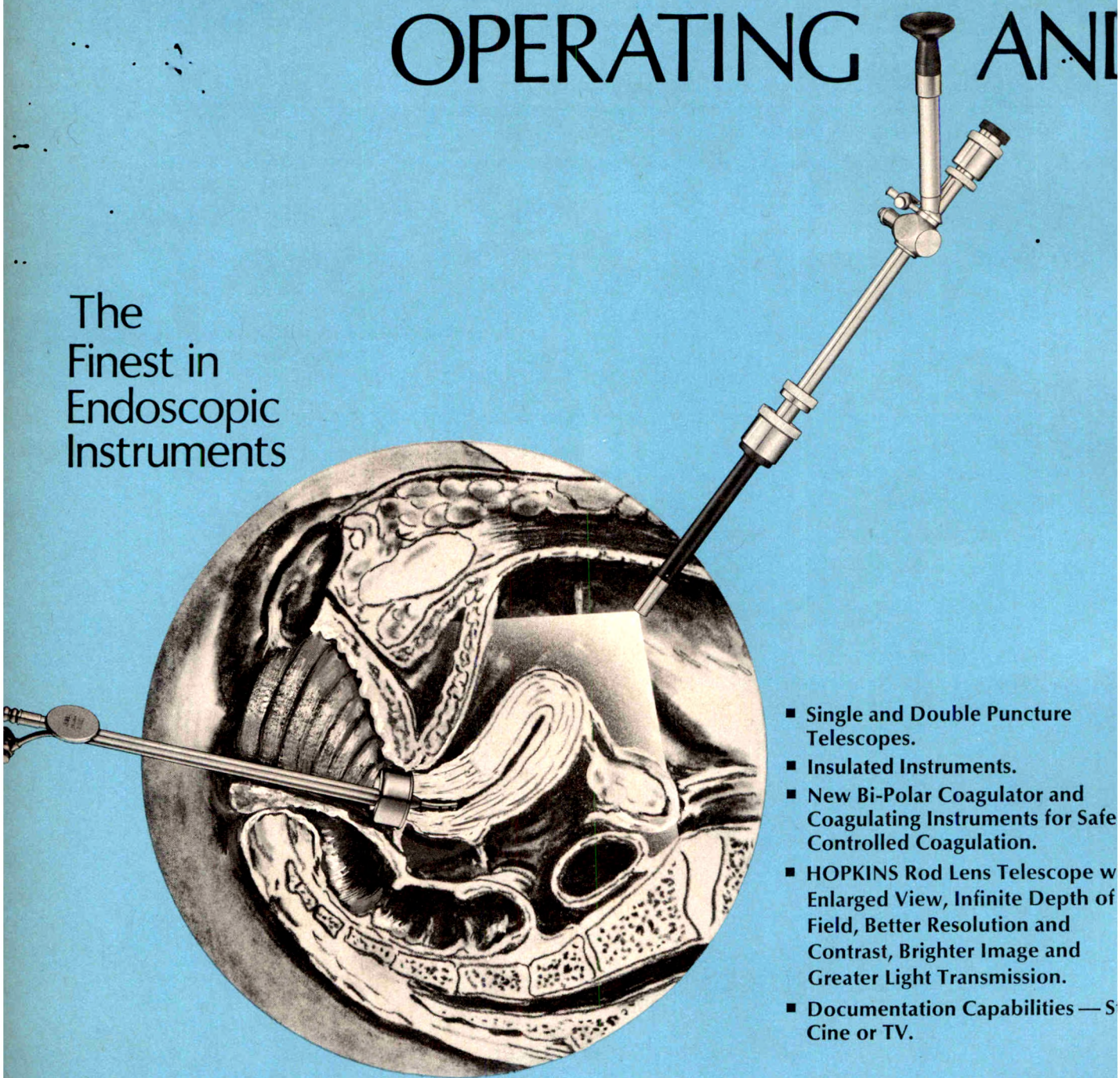
Please see complete product labeling for insertion and removal techniques.

SEARLE **Searle Laboratories**
Division of G D Searle & Co
Box 5110, Chicago, Illinois 60680

6BJ-R1

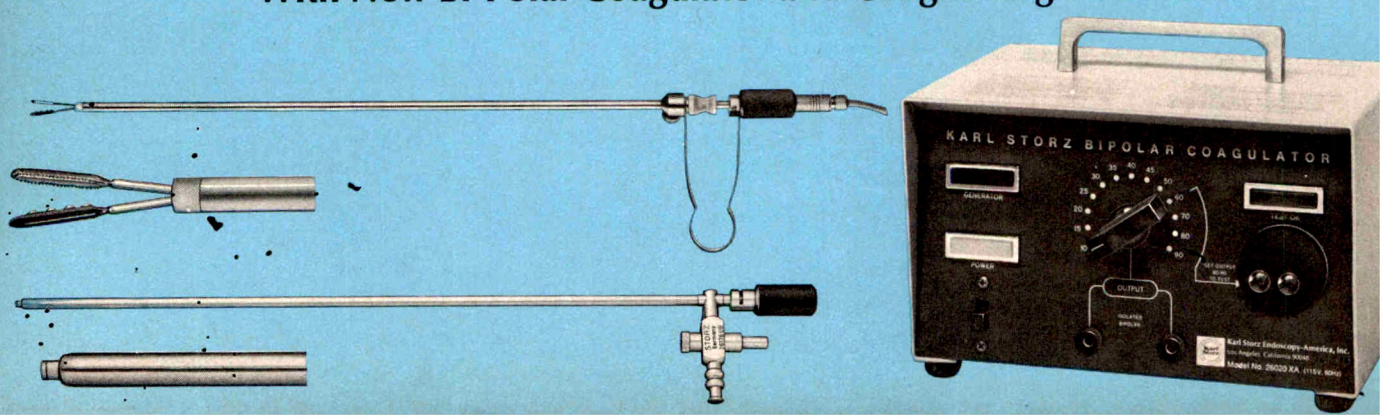
NEW LAPAROSCOPES! OPERATING AN

The Finest in Endoscopic Instruments

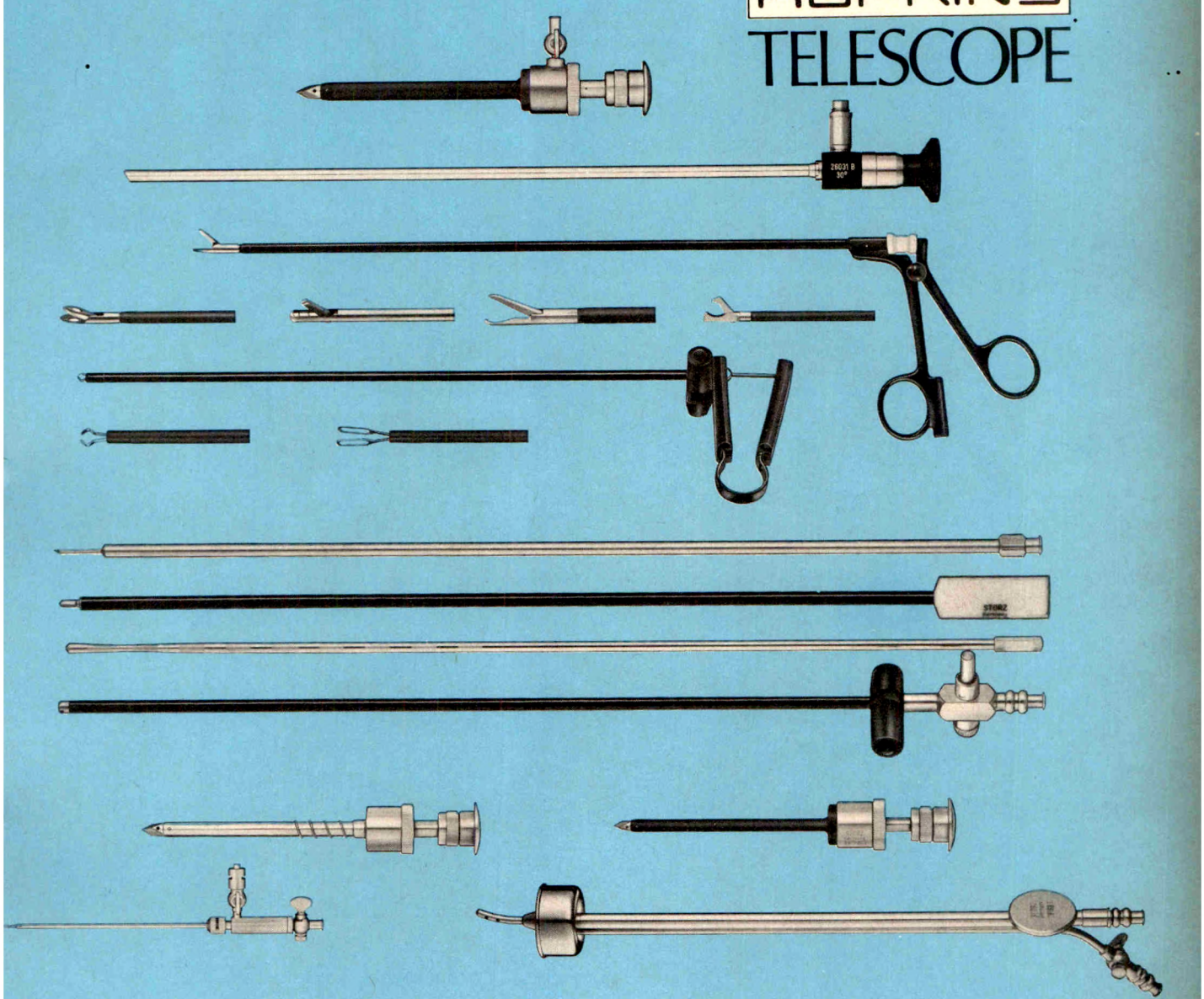


- Single and Double Puncture Telescopes.
- Insulated Instruments.
- New Bi-Polar Coagulator and Coagulating Instruments for Safe Controlled Coagulation.
- HOPKINS Rod Lens Telescope w Enlarged View, Infinite Depth of Field, Better Resolution and Contrast, Brighter Image and Greater Light Transmission.
- Documentation Capabilities — S Cine or TV.

With New Bi-Polar Coagulator and Coagulating Instruments



ENLARGED VIEW from Karl Storz with HOPKINS TELESCOPE



Karl Storz Endoscopy—America, Inc.
658 South San Vicente Blvd., Los Angeles, Ca. 90048

FOR TOLL FREE SERVICE 800-421-0837
(Except California) In Calif. CALL (213) 651-1068

Gentlemen:

☐ Please send me latest brochure and prices. ☐ Please have a Karl Storz Representative phone me for an appointment.

Thank you.

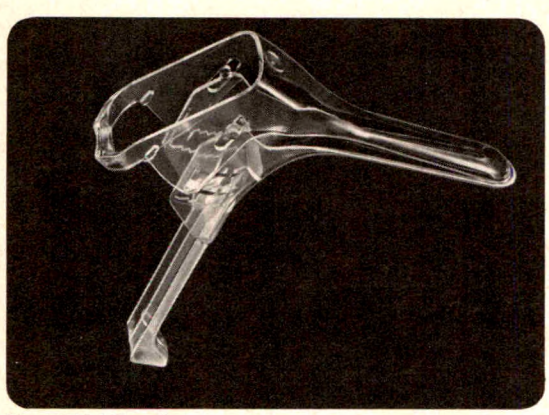
Name (please print)

Address

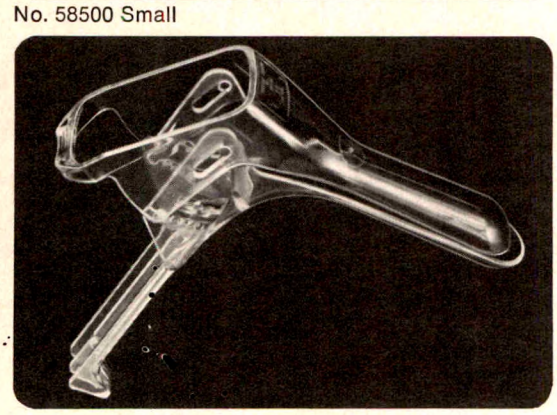
City State Zip



PRE-LUBRICATED disposable vaginal specula...now in two sizes.



No. 58500 Small



No. 58501 Regular

Just wet the new Welch Allyn KleenSpec® Pre-Lubricated Disposable Vaginal Specula with water—and they're ready for use!

Check these advantages:

- ☐ Compatible with Pap Smear procedures
- ☐ Easier insertion—minimizes trauma
- ☐ Speeds examinations—saves time
- ☐ No cleanup as with ordinary lubricants
- ☐ New small size specula have same advantages as the regular size
- ☐ Individually packaged—assures cleanliness and prevents cross-contamination
- ☐ One-hand operation—elevation plus angulation
- ☐ Built-in mucus barrier
- ☐ Optional fiber optic illuminator No. 78500

Contact your Authorized Welch Allyn Distributor TODAY!

WELCH ALLYN

WELCH ALLYN, INC. Skaneateles Falls, N. Y. 13153 U.S.A.

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

September 15
1976

Clinical opinion

Rational management of perinatal hydrocephalus 151
Peggy C. Ferry, M.D., and M. L. Pernoll, M.D.
Portland, Oregon, and Nashville, Tennessee

Choice of an oral contraceptive 153
Alvin Langer, M.D., Mona Devanesan, M.D., Marco A. Pelosi, M.D., Joseph J. Apuzzio, M.D., and Michael Frattarola, M.D.
Newark, New Jersey

Gynecology

Cul-de-sac isolates from patients with endometritis-salpingitis-peritonitis and gonococcal endocervicitis 158
Gilles R. G. Monif, M.D., Susan L. Welkos, Herman Baer, M.D., and Robert J. Thompson, M.D.
Jacksonville and Gainesville, Florida

(Contents continued on page 7)

Vol. 126, No. 2, September 15, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$37.00	$45.50	$47.00
Personal†	$27.00	$35.50	$37.00
Student, intern, resident†	$21.60	$30.10	$31.60

*(*Postal Union of the Americas and Spain)*

Single copies are $3.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.



Nude by Mario Korbel from Museum Pieces Inc.

True human estrogen replacement

Hormonin
(estriol, estradiol, estrone)

BRIEF SUMMARY: See package insert for full prescribing information.

CHOOSE FROM TWO CONVENIENT ORAL FORMS:

HORMONIN NO. 1 (half strength)	*HORMONIN NO. 2 (full strength)*
Each Tablet Contains:	*Each Tablet Contains:*
ESTRIOL 0.135 mg.	*ESTRIOL 0.27 mg.*
ESTRADIOL 0.3 mg.	*ESTRADIOL 0.6 mg.*
ESTRONE 0.7 mg.	*ESTRONE 1.4 mg.*

INDICATIONS: Replacement therapy for naturally occurring or surgically induced estrogen deficient states, including the menopause syndrome and post-menopausal conditions.

CONTRAINDICATIONS: Women having familial or personal history of mammary or genital cancer.

PRECAUTIONS: Estrogen should not be administered to women with recurrent mastitis or abnormal mammograms except in instances where the physician feels that treatment is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen dependent neoplasia.

The physician should be alert to the earliest manifestation of thrombotic disorders. Should this problem occur, discontinue estrogen therapy immediately. The long range effect of estrogen on nursing infants has not been established.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer of hypercalcemia, estrogen administration should be discontinued. The use of any estrogen in pregnancy is not recommended.

A complete pretreatment physical examination should be performed with special reference to the pelvis and breast. To avoid continuous stimulation of the uterus and breast, cyclic therapy is recommended (3 weeks on medication and 1 week off). Withdrawal bleeding may occur during the one week off medication. If unexplained or excessive vaginal bleeding occurs, the physician should check for the organic pathology.

Pre-existing fibromyomata may increase in size while using estrogen. For this reason, patients should be examined at regular intervals. Treatment with estrogen may mask the onset of the climacteric. Certain liver and endocrine function tests may be affected by exogenous estrogen administration.

DOSAGE: Orally, for the relief of menopausal symptoms, HORMONIN NO. 1, 1 or 2 tablets daily according to severity of symptoms; HORMONIN NO. 2, 1 tablet daily. The initial dosage may be decreased to establish maintenance dosage. To avoid possible continuous stimulation of the breast and uterus, cyclic therapy may be employed. In severe cases, initial therapy may be supplemented with parenteral estrogens.

CARNRICK LABORATORIES

DIV. G. W. CARNRICK CO., 65 HORSE HILL ROAD, CEDAR KNOLLS, N.J. 07927

Contents continued from page 5

The effect of L-dopa and chlorpromazine on prolactin and growth hormone secretion in normal women 162

H. Leblanc and S. S. C. Yen

La Jolla, California

Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause 165

Sezer Aksel, M.D., David W. Schomberg, Ph.D., Lee Tyrey, Ph.D., and Charles B. Hammond, M.D.

Durham, North Carolina

Scanning and transmission electron microscopic studies of vaginal adenosis and the cervical transformation zone in progeny exposed in utero to diethylstilbestrol 170

Cecilia M. Fenoglio, M.D., Alex Ferenczy, M.D., Ralph M. Richart, M.D., and Duane Townsend, M.D.

New York, New York, Montreal, Quebec, Canada, and Los Angeles, California

Hysterosalpingographic follow-up of laparoscopic sterilization 181

Hamid H. Sheikh, M.D.

Louisville, Kentucky

The significance of measurement of human placental lactogen, human chorionic gonadotropin, and carcinoembryonic antigen in patients with ovarian carcinoma 186

Naguib A. Samaan, M.D., Ph.D., Julian P. Smith, M.D., Felix N. Rutledge, M.D., and Pamela N. Schultz, B.S.

Houston, Texas

Dysgerminoma of the ovary: Radiation therapy for recurrence and metastases 190

Muhammad Ali Afridi, M.D., Vitune Vongtama, M.D., Yoshiaki Tsukada, M.D., and M. Steven Piver, M.D., F.A.C.O.G.

Buffalo, New York

Obstetrics

Maternal and fetal effects of lumbar epidural analgesia for labor and delivery in patients with gestational hypertension 195

Francis M. James III, M.D., and Paul Davies, Ph.D.

Birmingham, England

Response of human uterine arteries to local anesthetics 202

Luis A. Cibils, M.D.

Chicago, Illinois

(Contents continued on page 9)

In routine and resistant vaginal moniliasis...

MONISTAT CREAM
TRADEMARK

(MICONAZOLE NITRATE 2%)



significantly high cures after one course of therapy

high cure rates in the pregnant,† the non-pregnant, women on antibiotic therapy, women previously treated with other antifungal agents

negative cultures usually maintained 30 days or more post-therapy

usually works in one course of therapy with a simple once-daily h.s. dosage for 14 days

soothing, non-staining cream also may be used on external vulva

†Monistat Cream may be used in the second and third trimesters. However, in the first trimester, it should be used only when the physician considers it essential to the patient's welfare.

Description MONISTAT (miconazole nitrate 2%) is a water-miscible, white cream containing as the active ingredient, 2% miconazole nitrate, 1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy) phenethyl] imidazole nitrate.

Actions MONISTAT Cream exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown.

Indications MONISTAT Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis).

As MONISTAT Cream is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis*) should be ruled out by appropriate laboratory methods.

MONISTAT is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See PRECAUTIONS.)

Contraindication Patients known to be hypersensitive to this drug.

Precautions *General:* Discontinue drug if sensitization or irritation is reported during use. *Laboratory Tests:* If there is a lack of response to MONISTAT, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens. *Pregnancy:* MONISTAT Cream was used in 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women. Since MONISTAT Cream is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient.

Adverse Reactions Thirty-nine (7.4%) of the 528 patients treated with MONISTAT reported complaints during therapy that were possibly drug-related. Most complaints were reported during the first week of therapy. Vulvovaginal burning, itching or irritation occurred in 6.6%, while other complaints such as vaginal burning, pelvic cramps, hives, skin rash and headache occurred rarely (each less than 0.2% patient incidence). The therapy-related dropout rate was 0.9%.

Dosage and Administration One applicatorful is administered intravaginally once daily at bedtime for 14 days. Course of therapy may be repeated after other pathogens have been ruled out by appropriate smears and cultures.

Supplied MONISTAT Cream is available in 3 oz. (85 g) tubes with Ortho* Measured Dose Applicator.

MONISTAT (Miconazole Nitrate 2%) is a development of Ortho Pharmaceutical Corporation and Janssen Pharmaceutica, Belgium.

*TRADEMARK

© OPC 1976

OJ260-5R2

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Contents continued from page 7

Placental function and renal tract studies in pre-eclampsia with proteinuria and long-term maternal consequences 211
John R. H. Fliegner, M.D.
Melbourne, Victoria, Australia

Reduction of the stretch modulus of human cervical tissue by prostaglandin E_2 218
John T. Conrad, Ph.D., and Kent Ueland, M.D.
Seattle, Washington

Spontaneous contractility and the response of the human uterine cervix to prostaglandins $F_{2\alpha}$ and E_2 during the menstrual cycle 224
Elsimar M. Coutinho, M.D., and Elias Darzé, M.D.
Salvador, Bahia, Brazil

Bacteriologic effects of prophylactic antibiotics in cesarean section 226
Ronald S. Gibbs, M.D., and Allan J. Weinstein, M.D.
Philadelphia, Pennsylvania

Abnormal adolescent primiparous pregnancy: Association of race, human chorionic somatomammotropin production, and smoking 230
Dorothy R. Hollingsworth, M.D., Russel J. Moser, Ph.D., Jay W. Carlson, B.S., and Kathryn T. Thompson, B.A.
Lexington, Kentucky

Measurement of the pre-ejection period during labor with the use of arterial pulse time 238
A. Bernstein, M.D., L. W. Organ, M.D., B.A.Sc., L. E. Eisner, M.A.Sc., K. C. Smith, Ph.D., and I. H. Rowe, Ph.D.
Toronto, Ontario, Canada

Observations on maternal oxytocin release during human labor and the effect of intravenous alcohol administration 243
G. L. D. Gibbens, M.R.C.O.G., and T. Chard, M.D., M.R.C.O.G.
London, England

Fetus, placenta, and newborn

Needle puncture of fetus: A complication of second-trimester amniocentesis 247
Diane L. Broome, M.D., Miriam G. Wilson, M.D., Bennett Weiss, M.D., and Bonnie Kellogg, P.H.N.
Los Angeles, California

Circulatory response to atropine in sheep fetus 253
Tsuyomu Ikenoue, M.D., Edward J. Quilligan, M.D., and Yuji Murata, M.D.
Los Angeles, California

(Contents continued on page 11)



Fast, accurate information . . .

when you need it, wherever you need it, from Sonicaid's battery powered, portable, fetal heart detectors.
Sonicaid also manufactures a comprehensive line of AC powered fetal heart detectors and fetal/maternal monitors. Write or phone Executive Vice President John Scales today for complete information.

D205 Portable Diagnostic Fetal Heart Detector
directional, ultra-sound transducer's output fed to stethoscope-style headset, loudspeaker or tape recorder.



SONICAID

P.O. Box 714 Fredericksburg, VA 22401 (703) 898-6820 Telex 827304

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 339, Erie, Pennsylvania 16512.



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼″ × 11″) for 1975 copies**
☐ **OLD SIZE (7¼″ × 10½″) for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____

Contents continued from page 9

In vitro perfusion of human placenta. V. Oxygen consumption 261
Jean-Claude Challier, Ph.D., Henning Schneider, M.D., and Joseph Dancis, M.D.
New York, New York

The significance of fetal electrocardiography in the diagnosis of intrauterine bradyarrhythmia 266
E. G. Abinader, M.D., A. Klein, M.D., I. Eibschitz, M.D., A. Zilberman, M.D., B. Pezeshk, M.D., and M. Sharf, M.D.
Haifa, Israel

Moderate fetal bradycardia 271
Bruce K. Young, M.D., F.A.C.O.G., and Howard M. Weinstein, M.D.
New York, New York

Umbilical vein occlusion and transient acceleration of the fetal heart rate 276
L. Stanley James, M.D., Ming-Neng Yeh, M.D., Hisayo O. Morishima, M.D., Ph.D., Salha S. Daniel, Ph.D., Steve N. Caritis, M.D., Wendell H. Niemann, D.V.M., and Leonard Indyk, Ph.D.
New York, New York

Classic pages

Classic pages 284

Communications in brief

Listeriosis during pregnancy 285
Yong Hyen Hwang, M.D., F.A.C.O.G.
Salisbury, Maryland

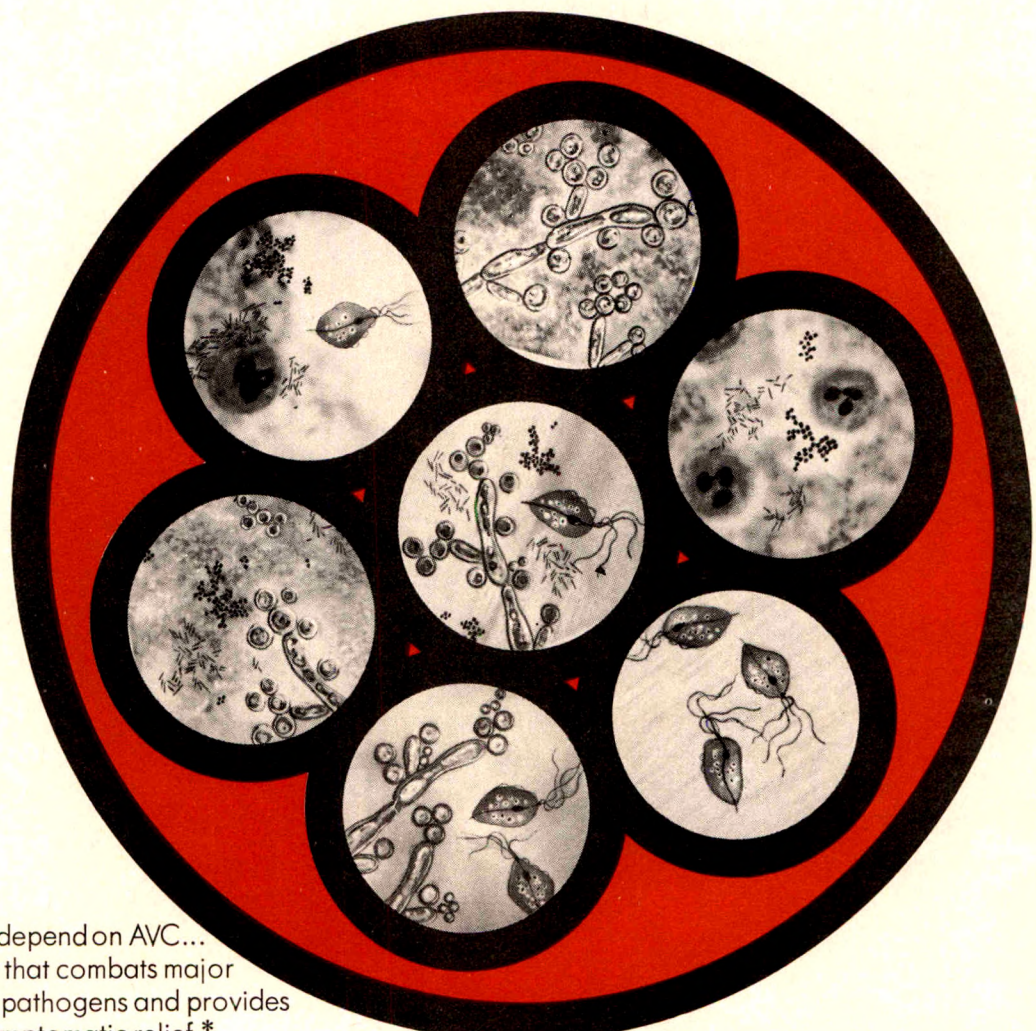
Pelvic inflammatory pseudotumor: A case report 286
Pravit Kunakemakorn, M.D., Gordon Ontai, M.D., and Howard Balin, M.D.
Philadelphia, Pennsylvania

Prenatal diagnosis by fetoscopy with subsequent normal delivery: Report of a case 287
Ronald J. Benzie, M.D., Ch.B., M.R.C.O.G., F.R.C.S.(C), Ralph M. Malone, M.B., Ch.B., M.R.C.O.G., Murray Miskin, M.D., F.R.C.S.(C), Noreen L. Rudd, M.D., F.R.C.P.(C), and Philip A. Schofield, M.B., Ch.B., C.C.F.P.
Toronto, Ontario, Canada

Ultrasonic measurement of cervical dilatation during labor 288
Frans Th. Kok, M.D., Henk C. S. Wallenburg, M.D., Ph.D., and Juriy W. Wladimiroff, M.D., Ph.D.
Rotterdam, The Netherlands

(Contents continued on page 13)

The causes of vaginitis are multiple



You can depend on AVC... therapy that combats major vaginal pathogens and provides rapid symptomatic relief.*

*__Indications:__ Based on a review of AVC by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually *Trichomonas vaginalis*, *Candida albicans*, or *Hemophilus vaginalis*) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

__Contraindications:__ Known sensitivity to sulfonamides.
__Precautions/Adverse Reactions:__ The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.
__Dosage:__ 1 applicatorful (about 6 g.) or 1 suppository intravaginally once or twice daily.
__Supplied:__ Cream–4 ounce tube with applicator. Suppositories–Box of 16 with inserter.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

4-6744 (6049)

The treatment is singular

AVC™

__Cream__ (aminacrine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%)

__Suppositories__ (aminacrine hydrochloride 0.014 g., sulfanilamide 1.05 g., allantoin 0.14 g.)

Contents continued from page 11

Antepartum detection of congenital complete fetal heart block: A case report 291
David H. Armstrong, M.D., Yuji Murata, M.D., Chester B. Martin, Jr., M.D., and Tsuyomu Ikenoue, M.D.
Los Angeles, California

Rectouterine fistula associated with the Cu-7 intrauterine contraceptive device 292
R. D. Patchell, M.D.
Charleston, West Virginia

Ultrasound localization of laminaria 293
Timothy G. Lee, M.D., and Donald C. Barnett, M.D.
Portland, Oregon

Correspondence

Correspondence 296

Books

Books received 300

(Information for authors on page 25)

For the special needs of patients with hard, dry stools

Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT S Tablets offer comfortable relief by softening the stool *and* stimulating its movement.

Provides standardized senna concentrate, a clinically established laxative of choice
Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

Provides DSS, the classic stool softener
DSS in SENOKOT S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime SENOKOT S Tablets usually induce predictable, comfortable evacuation the next morning.

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8339 178576

Senokot® S tablets

(standardized senna concentrate and dioctyl sodium sulfosuccinate)

the "S" stands for softener





Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

Advisory committee on policy

David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

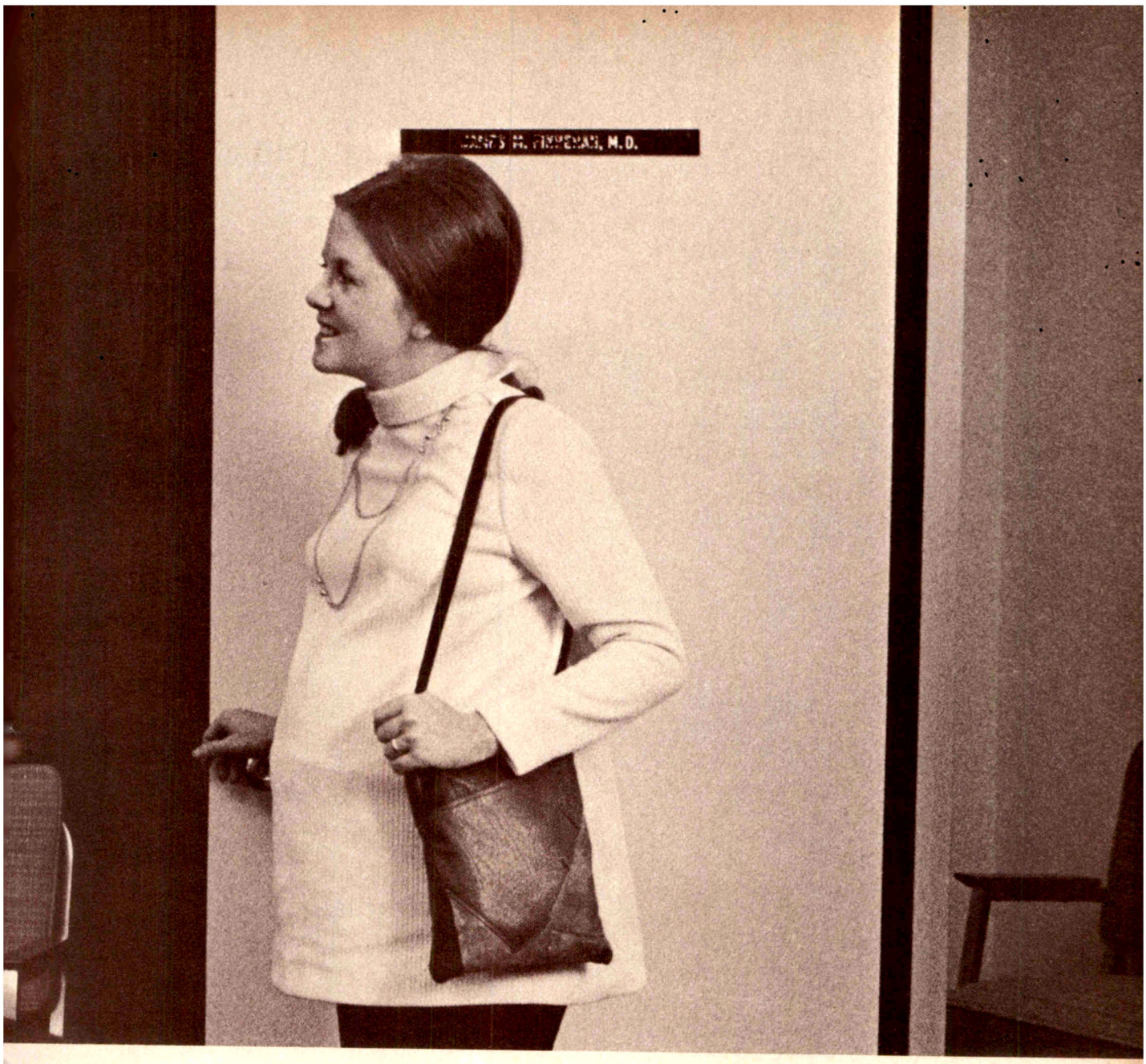
Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*



Abbott hematinics can help to provide optimum care to term

- These are the only major products containing the exact U.S. RDA* of folic acid for pregnancy—800 mcg.
- Dosage is one-a-day—helps to assure patient cooperation.
- To minimize gastric upset, each product contains 525 mg. of Ferrous Sulfate in controlled-release form—an important consideration in pregnancy.
- Both products contain 500 mg. of Vitamin C to enhance iron absorption.

*Federal Register, 38:20717, Aug. 2, 1973.



Fero-Folic-500® ℞

Controlled-Release Iron
525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption
500 mg. Ascorbic Acid (as sodium ascorbate)

Plus 800 mcg. of Folic Acid

Indications: For the treatment of iron deficiency and prevention of concomitant folic acid deficiency in non-pregnant adults. Also indicated in pregnancy for the prevention and treatment of iron deficiency and to supply a maintenance dosage of folic acid. **Contraindications:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Fero-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

Iberet-Folic-500® ℞

Controlled-Release Iron
525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption
500 mg. Ascorbic Acid (as sodium ascorbate)

Plus the B-Complex
Niacinamide, 30 mg.; Calcium Pantothenate, 10 mg.; Vitamin B_1 (Thiamine Mononitrate), 6 mg.; Vitamin B_2 (Riboflavin), 6 mg.; Vitamin B_6 (Pyridoxine Hydrochloride), 5 mg.; Vitamin B_{12} (Cyanocobalamin), 25 mcg.

Plus 800 mcg. of Folic Acid

Indications: In non-pregnant adults, for the treatment of iron deficiency and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins. Also indicated in pregnancy for the prevention and treatment of iron deficiency where there is a concomitant deficient intake or increased need for B-complex vitamins (including folic acid). **Contraindication:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Iberet-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. 6033133

ABBOTT

MOSBY
TIMES MIRROR

If you're
concerned with
cancer treatment,
turn to the
fact-filled new
edition of this
comprehensive reference

New 2nd Edition!

THE IMMUNOLOGY OF MALIGNANT DISEASE

More than tripling the size of its previous edition, this outstanding revision provides you with the most current information available on immunologic reactions, diseases and therapies of man. Combining pertinent clinical data with laboratory research findings, the authors examine cellular events involved in the normal human immune response, explore how they become disordered in malignancy, and consider what may be done to correct these disorders. An especially valuable chapter will acquaint you with the important groundwork that has led to practical applications of tumor immunology in humans, based on data derived from experimental animal studies. Other informative chapters offer you specific methods for measurement and quantitation of immune function in humans and discuss investigational immunotherapy of human tumors.

By Jules E. Harris, M.D., F.R.C.P.(C), F.A.C.P. and Joseph G. Sinkovics, M.D., F.A.C.P. August, 1976. 2nd edition, approx. 704 pages, 7 "× 10 ", 36 illustrations. About $42.50.

MOSBY
TIMES MIRROR

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

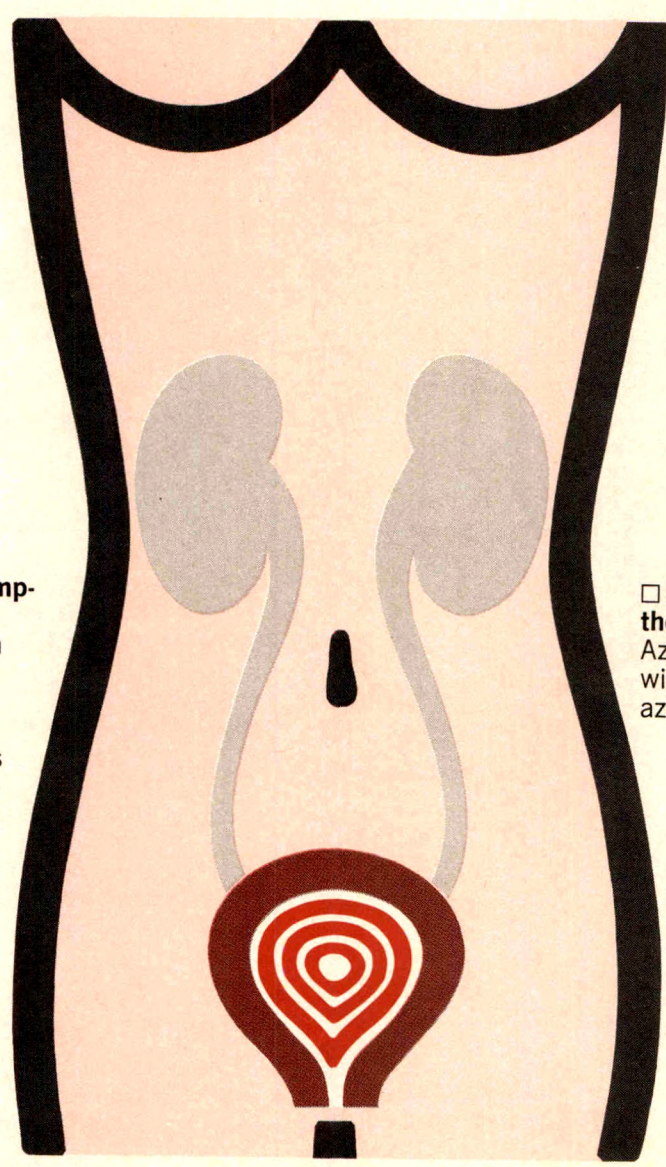
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

When pain complicates acute cystitis*

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain for the pathogens



☐ **Early relief of painful symptoms** such as burning and discomfort associated with urgency and frequency.

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

☐ **Appropriate antibacterial therapy:** up to three days with Azo Gantanol, then 11 days with Gantanol® (sulfamethoxazole).

*nonobstructed; due to susceptible organisms

ROCHE

PERINATAL MEDICINE

offered by

UNIVERSITY OF SOUTHERN CALIFORNIA
School of Medicine—Postgraduate
Division and Department of
Obstetrics and Gynecology

January 29—February 4, 1977
at
The Royal Lahaina Hotel on the
Island of Maui

This course is intended to provide up-to-date information in perinatal medicine; emphasis will be placed on usage of the newer techniques which evaluate perinatal condition and how these are used in clinical care.

Faculty includes A. W. Liley, M.D., KCMG, The University of Auckland, New Zealand; Abraham M. Rudolph, M.D., University of California, San Francisco; Richard H. Paul, M.D., Edward H. Hon, M.D., William J. Ledger, M.D., Edward J. Quilligan, M.D., and other distinguished faculty members of the University of Southern California.

Tuition: $275. To enroll or to request further information, use the following form and mail to: Associate Dean, USC School of Medicine, Postgraduate Division, 2025 Zonal Avenue, Los Angeles, California 90033, Phone (213) 226-2051.

Please enroll me (check enclosed) _____

Please send further information _____

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

(PERINATAL MEDICINE #144)

MOSBY
TIMES MIRROR

Announcing!

A new edition offers you the most up-to-date knowledge and procedures available in perinatal care.

New 2nd Edition!

MEDICAL CARE OF THE SICK NEWBORN

Emphasizing the team approach to perinatal care, this outstanding new edition offers you and your staff the most current perinatal knowledge and procedures available. You'll find every section of the book focuses on the delivery of coordinated health care to the newborn. Offering clear, practical guidelines, Part I discusses organization and administration of newborn services. Part II covers factors which affect management of the newborn and general management of the neonate, clinical assessment, recognition of specific conditions and treatment. Of special importance is the chapter on respiratory distress syndrome. This chapter has been virtually rewritten to reflect the massive amount of new knowledge developed in this area since the previous edition. Why not add this new edition to your professional library?

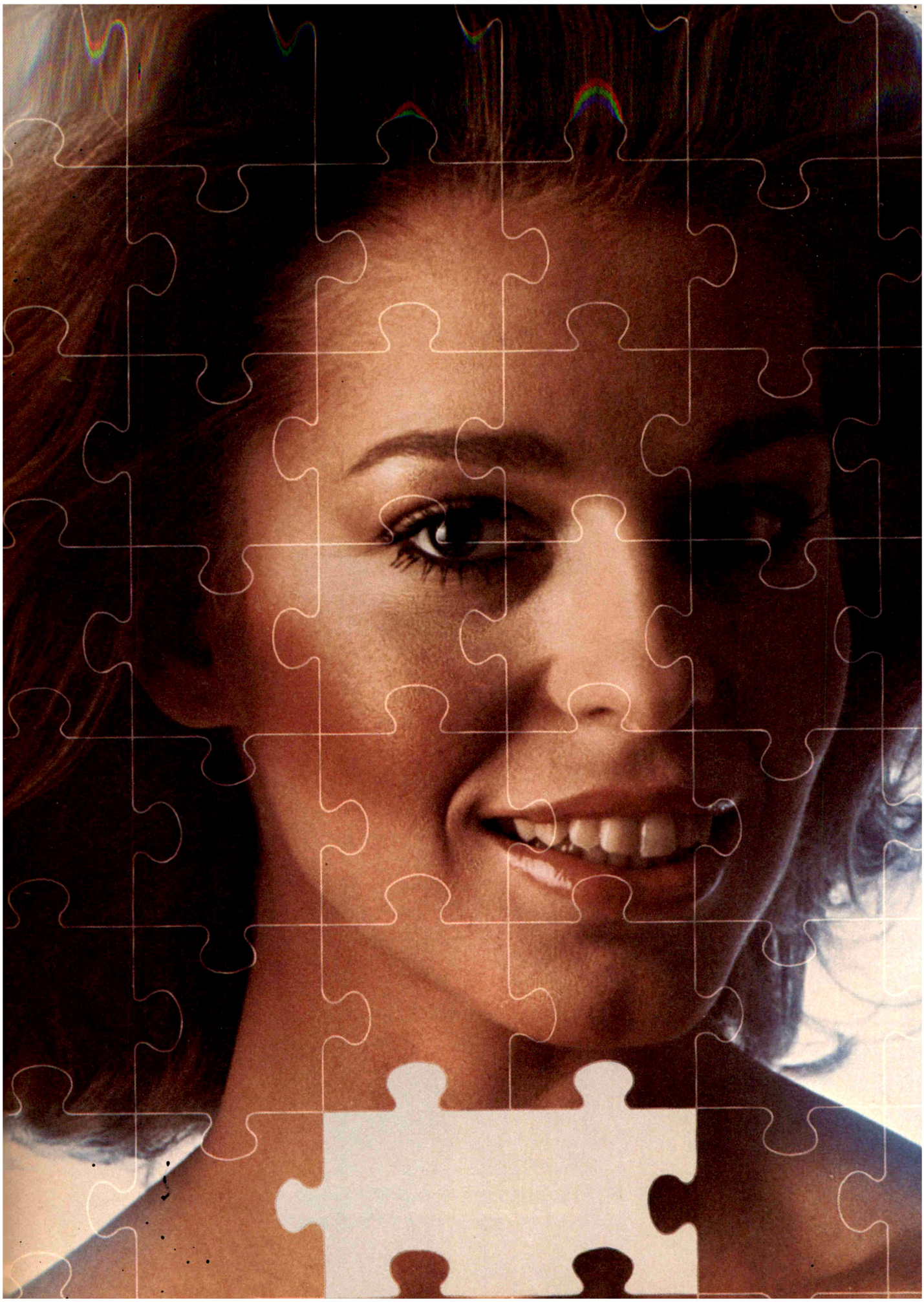
By Sophie H. Pierog, M.D. and Angelo Ferrara, M.D. September, 1976. 2nd edition, approx. 336 pages, 6″ × 9″, 70 illustrations. About $14.50.

MOSBY
TIMES MIRROR
THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY



the unpuzzling approach to thyroid replacement therapy

SYNTHROID® (Sodium Levothyroxine, U.S.P.) Flint is not derived from any animal gland source. It is a pure synthetic. Every batch of SYNTHROID (Sodium Levothyroxine) is of controlled potency. And, it provides your patients with everything they need for complete thyroid replacement therapy.

T4, T3, or both? SYNTHROID (Sodium Levothyroxine, U.S.P.) Flint is T4 which is converted to T3 at the cellular level, providing a physiologic source and optimal amount of T3 to meet metabolic needs for your hypothyroid patients. Because of the slower and steadier onset of action, the possibility of sudden metabolic surges is reduced with SYNTHROID therapy.

SYNTHROID medication is practical and economical for long-term therapy. A recent study of 44 hypothyroid patients indicates that 89 percent were maintained with doses of T4 (SYNTHROID) between 100 mcg. and 200 mcg. (0.1 mg. and 0.2 mg.) per day.[1]

If you're interested in additional information, we'd be pleased to send you a portfolio of pertinent clinical data. Write or contact your Flint representative.



Synthroid®
(Sodium Levothyroxine, U.S.P.) Flint

See reverse side for full prescribing information

1. Stock, J. M., Surks, M. I., and Oppenheimer, J. H. Replacement dosage of L-thyroxine in hypothyroidism. A re-evaluation. New Engl. J. Med. 290:529-33, 1974.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Synthroid®

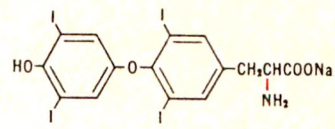
(Sodium Levothyroxine. U.S.P.) Flint

Eliminates many of the uncertainties of desiccated thyroid therapy



Synthroid Tablets—for oral administration
Synthroid for Injection—for parenteral administration

Description: SYNTHROID (sodium levothyroxine) **Tablets** and SYNTHROID **Injection** contain synthetic crystalline sodium levothyroxine (L-thyroxine). L-thyroxine is the principal hormone secreted by the normal thyroid gland.



Sodium Levothyroxine

Actions: SYNTHROID (sodium levothyroxine) **Tablets,** taken orally, provide hormone that is readily absorbed from the gastrointestinal tract. SYNTHROID **Injection** is effective by any parenteral route. Following absorption, the synthetic L-thyroxine provided by SYNTHROID products cannot be distinguished from L-thyroxine that is endogenously secreted. Each is bound to the same serum proteins and each exhibits a six to seven day circulating half-life in the euthyroid individual.

Both SYNTHROID products will provide L-thyroxine as a substrate for physiologic deiodination to L-triiodothyronine. Therefore, patients taking SYNTHROID products will demonstrate normal blood levels of L-triiodothyronine even when the thyroid gland has been surgically removed or destroyed by radioiodine. Administration of levothyroxine alone will result in complete physiologic thyroid replacement.

Indications: SYNTHROID (sodium levothyroxine) products serve as specific replacement therapy for reduced or absent thyroid function of any etiology. SYNTHROID **Injection** can be used intravenously whenever a rapid onset of effect is critical, and either intravenously or intramuscularly in hypothyroid patients whenever the oral route is precluded for long periods of time.

Contraindications: There are no absolute contraindications to SYNTHROID (sodium levothyroxine) therapy. Relative contraindications include acute myocardial infarction, uncorrected adrenal insufficiency and thyrotoxicosis. (See WARNINGS)

Warnings: Patients with cardiovascular diseases warrant particularly close attention during the restoration of normal thyroid function by any thyroid drug. In such cases, low initial dosage increased slowly by small increments is indicated. Occasionally, the cardiovascular capacity of the patient is so compromised that the metabolic demands of the normal thyroid state cannot be met. Clinical judgment will then dictate either a less-than-complete restoration of thyroid status or reduction in thyroid dosage.

Endocrine disorders such as diabetes mellitus, adrenal insufficiency (Addison's disease), hypopituitarism and diabetes insipidus are characterized by signs and symptoms which may be diminished in severity or obscured by hypothyroidism. SYNTHROID (sodium levothyroxine) therapy for such patients may aggravate the intensity of previously obscured symptoms and require appropriate adjustment of therapeutic measures directed at these concomitant disorders.

Thyroid replacement may potentiate the effects of anticoagulants. Patients on anticoagulant therapy should have frequent prothrombin determinations when instituting thyroid replacement to gauge the need to reduce anticoagulant dosage.

Precautions: Overdosage with any thyroid drug may produce the signs and symptoms of thyrotoxicosis, but resistance to such factitious thyrotoxicosis is the general rule. With SYNTHROID (sodium levothyroxine) **Tablets,** the relatively slow onset of action minimizes the risk of overdose but close observation in the weeks following institution of a dosage regimen is advised. Treatment of thyroid hyperactivity induced by oral medication is confined to interruption of therapy for a week, followed by reinstitution of daily therapy at an appropriately reduced dosage.

Adverse reactions: Adverse reactions are due to overdose and are those of induced hyperthyroidism.

Dosage and administration: For most adults, a final dosage of 100 mcg (0.1 mg) to 200 mcg (0.2 mg) of SYNTHROID (sodium levothyroxine) **Tablets** daily will restore normal thyroid function and only occasionally will patients require larger doses. Failure to respond adequately to a daily oral intake of 400 mcg (0.4 mg) or more is rare and should prompt reconsideration of the diagnosis of hypothyroidism, special investigation of the patient in terms of malabsorption of L-thyroxine from the gastrointestinal tract or poor adherence to therapy.

The concomitant appearance of other diseases, especially cardiovascular diseases, usually dictates a replacement regimen with initial doses smaller than 100 mcg/day (0.1 mg).

In otherwise healthy adults with relatively recent onset of hypothyroidism, full replacement dose of 150 mcg (0.15 mg) or 200 mcg (0.2 mg) has been instituted immediately without untoward effect and with good therapeutic response. General experience, however, favors a more cautious approach in view of the possible presence of subclinical disorders of the cardiovascular system or endocrinopathies.

The age and general physical condition of the patient as well as the severity and duration of hypothyroid symptoms determine the starting dosage and the rate of incremental dosage increase leading to a final maintenance dosage. In the elderly patient with long standing disease, evidence of myxedematous infiltration and symptomatic, functional or electrocardiographic evidence of cardiovascular dysfunction, the starting dose may be as little as 25 mcg (0.025 mg) per day. Further incremental increases of 25 mcg (0.025 mg) per day may be instituted at three to four week intervals depending on patient response. Conversely, otherwise healthy adults may be started at higher daily dosage and raised to the full replacement dosage in two to three weeks. Clearly it is the physician's judgment of the severity of the disease and close observation of patient response which determines the rate of dosage titration.

Laboratory tests to monitor thyroid replacement therapy are of limited value. Although measurement of normal blood levels of thyroxine in patients on replacement regimens frequently coincides with the clinical impression of normal thyroid status, higher than normal levels on oral replacement of levothyroxine occasionally occur and should not be considered evidence of overdosage per se.

In all cases, clinical impression of the well-being of the patient takes precedence over laboratory determination in determining the appropriate individual dosage.

In infants and children, there is a great urgency to achieve full thyroid replacement because of the critical importance of thyroid hormone in sustaining growth and maturation. Despite the smaller body size, the dosage needed to sustain a full rate of growth, development and general thriving is higher in the child than in the adult, as much as 300 mcg (0.3 mg) to 400 mcg (0.4 mg) per day.

In myxedema coma or stupor, without concomitant severe heart disease, 200 to 500 mcg of SYNTHROID **Injection** may be administered intravenously as a solution containing 100 mcg/ml. Although the patient may show evidence of increased responsivity within six to eight hours, full therapeutic effect may not be evident until the following day. An additional 100 to 300 mcg or more may be given on the second day if evidence of significant and progressive improvement has not occurred. Like the oral dosage form, SYNTHROID **Injection** produces a predictable increase in the circulating level of hormone with a long half-time. This usually precludes the need for multiple injections but continued daily administration of lesser amounts intravenously should be maintained until the patient is fully capable of accepting a daily oral dose.

In the presence of concomitant heart disease, the sudden administration of such large doses of L-thyroxine intravenously is clearly not without its cardiovascular risks. Under such circumstances, intravenous therapy should not be undertaken without weighing the alternative risks of the myxedema coma and the cardiovascular disease. Clinical judgment in this situation may dictate smaller intravenous doses of levothyroxine.

SYNTHROID **Injection** by intravenous or intramuscular routes can be substituted for the oral dosage form when ingestion of SYNTHROID **Tablets** is precluded for long periods of time.

How Supplied: SYNTHROID (sodium levothyroxine) **Tablets** are supplied as scored, color-coded compressed tablets in 6 concentrations: 25 mcg (0.025 mg)—orange . . . 50 mcg (0.05 mg)—white . . . 100 mcg (0.1 mg)—yellow . . . 150 mcg (0.15 mg)—blue . . . 200 mcg (0.2 mg)—pink . . . 300 mcg (0.3 mg)—green.

SYNTHROID (sodium levothyroxine) for **Injection** is supplied in 10 ml vials containing 500 mcg of lyophilized active ingredient and 10 mg of Mannitol, U.S.P. A separate 5 ml vial containing Sodium Chloride Injection, U.S.P. is provided as a diluent.

Directions for reconstitution: Reconstitute the lyophilized sodium levothyroxine by aseptically adding 5 ml of the Sodium Chloride Injection, U.S.P. to the vial. Shake vial to insure complete mixing. **Use immediately** after reconstitution. Discard any unused portion.

U.S. Pat. 2,889,363

January 1975

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

American Journal of Obstetrics and Gynecology
Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2,* Current Investigation and Clinical Opinion, limited to *6,* and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. 2:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. 2:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll, R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. 3:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 2 SEPTEMBER 15, 1976

CLINICAL OPINION

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to six citations. Mail to Frederick P. Zuspan, M.D., Editor.

Rational management of perinatal hydrocephalus

PEGGY C. FERRY, M.D.

M. L. PERNOLL, M.D.

Portland, Oregon, and Nashville, Tennessee

Hydrocephalus of prenatal origin, which may be hereditary, is likely to be discovered more frequently and earlier in gestation with ultrasonic diagnosis. It is suggested that each case be analyzed according to a protocol which includes a full obstetric evaluation, complete genetic pedigree, determination of familial cranial size, and complete neuropathologic study. Destruction of the aqueductal area may deprive the investigator of much of the information needed for the thorough study of the case which is vital to counsel the parents concerning future pregnancies.

MARKED hydrocephalus of prenatal origin occurs in approximately 0.2 per cent of all deliveries. Developmental malformations (aqueductal stenosis, the Arnold-Chiari malformation, the Dandy Walker syndrome, and other dysplastic lesions) may account for the majority of cases. However, as noted in a pediatric neurology text, "the cause of hydrocephalus in this category has not been studied in detail."[1] Indeed, it may now be appropriate to do a more formal study of each case because of the hereditary nature of x-linked aqueductal stenosis[2] and the autosomal recessive forms of aqueductal stenosis.[3]

Certainly the possibility of one of these hereditary forms of aqueductal stenosis should be considered in all infants who present with congenital hydrocephalus without associated meningomyocele. Moreover, recent refinements in ultrasonic encephalography make possible intrauterine detection of ventricular enlargement and more precise diagnosis of hydrocephalus. This advance may increase the early diagnosis of obstructive hydrocephalus and deepen the obstetric management dilemma because in many instances fetuses found to have hydrocephalus at or near birth are delivered via

From the Division of Perinatal Medicine, University of Oregon Health Sciences Center, and the Division of Child Development, Department of Pediatrics, Vanderbilt University School of Medicine.

Reprint requests: M. L. Pernoll, M.D., Head, Division of Perinatal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Rd., Portland, Oregon 97201.

destructive craniotomy. This procedure often makes it impossible to do a careful examination of the infant and study the underlying neuropathologic substrate for the type of hydrocephalus. Yet appropriate genetic counseling for the affected families mandates these careful examinations. Furthermore, isolated aqueductal stenosis may not always be associated with severe intellectual impairment if treated early. Advances in neurosurgical treatment of hydrocephalus make it possible for these children to survive for long periods and it is conceivable that the intellectual potential of some may be normal.[4]

For the purposes of studying perinatal hydrocephalus in more detail, to enable physicians to give parents more exact diagnoses, prognoses, and recurrence risks, we suggest the following protocol for suspected perinatal hydrocephalus:

1. Obtain thorough obstetric information, including:
   a. complications of pregnancy,
   b. possible viral infections,
   c. complications of labor (particularly meconium staining or undue prolongation of labor),
   d. maternal toxoplasmosis and cytomegalic inclusion disease titers,
   e. any fetal measurements (including ultrasonic),
   f. fetal maturity,
   g. length of gestation.
2. Obtain a complete genetic pedigree.
3. Measure the head circumference of both parents and any available siblings or relatives.
4. Perform complete physical and neurologic evaluation of the neonate to include:
   a. Apgar scores at 1 and 5 minutes,
   b. head circumference,
   c. length and weight measurements,
   d. presence or absence of other anomalies,
   e. skull x-ray,
   f. serum titers for toxoplasmosis and cytomegalic inclusion disease (and others as appropriate),
   g. photographs,
   h. genetics consultation and chromosomal analysis (if deemed appropriate).
5. If intracranial diagnostic studies and/or surgery are performed, complete details of these findings should be obtained.
6. If the infant dies or is delivered stillborn, complete neuropathologic studies, including the upper brain stem and spinal cord, should be performed by a neuropathologist after formalin fixation. Specific observations are necessary to determine:
   a. the exact type of hydrocephalus,
   b. the point of obstruction,
   c. detailed anatomy of the aqueduct of Sylvius and other associated cranial and spinal anomalies.
7. Finally, results of the genetic and neuropathologic studies should be communicated to the parents so that they may be aware of the risks for subsequent pregnancies.

It has been estimated that 2 per cent of all cases of uncomplicated hydrocephalus are x-linked. The empiric risk in these sporadic cases has been calculated to be 0.5 to 1.0 per cent. In the x-linked form, if there have been other affected brothers and/or male maternal relatives, a 25 per cent recurrence risk exists for each subsequent pregnancy and a 50 per cent risk exists that any subsequent male will be affected. In the autosomal recessive form, parents should be counseled that the chance for the mother to be a carrier of this gene is small, but the recurrence risk may be as high as 25 per cent in all future pregnancies.
future pregnancies.

Certainly the ultimate decision for management of perinatal hydrocephalus should be derived with full parental participation. In some circumstances cesarean section may be indicated to maximize the opportunity for survival through subsequent early operative treatment. However, should circumstances dictate a vaginal delivery with cerebral decompression, we suggest that useful information for counseling may be obtained if the aqueductal area is not destroyed and the hydrocephalus is investigated in an orderly fashion.

REFERENCES

1. Dekaban, A.: Neurology of Early Childhood, Baltimore, 1970, The Williams & Wilkins Company, p. 205.
2. Holmes, L. B., Nash, A., ZuRhein, G. M., et al.: X-linked aqueductal stenosis: Clinical and neuropathological findings in two families, Pediatrics **51:** 697, 1973.
3. Mehne, R. G.: Three hydrocephalic newborns, Arch. Pediatrics **78:** 67, 1961.
4. Mealey, J., Jr., Gilmore, R. L., and Bubb, M. P.: The prognosis of hydrocephalus overt at birth, J. Neurosurg. **39:** 348, 1973.

Choice of an oral contraceptive

ALVIN LANGER, M.D.
MONA DEVANESAN, M.D.
MARCO A. PELOSI, M.D.
JOSEPH J. APUZZIO, M.D.
MICHAEL FRATTAROLA, M.D.
Newark, New Jersey

The principles underlying pill usage are reviewed and a plan is suggested for initiation of therapy and patient follow-up.

SINCE THE marketing of the first oral contraceptive in 1961, and the subsequent acceptance of this method of birth control by a large number of women, a variety of types and dosage of hormones used in the pill have been developed. The introduction of new pills has been with the intent of decreasing risk or side effects, most often by decreasing dose. It is estimated that currently over 20 million women world-wide use the pill and that in the United States approximately 20 per cent of the women in the reproductive age are using these potent pharmacologic agents. This paper reviews the principles underlying pill usage and suggests a plan of initiation of therapy and patient follow-up.

Pharmacology and biochemistry

A knowledge of pharmacologic properties of the components is necessary in order to prescribe a suitable oral contraceptive. The hormones contained in oral contraceptives are synthetic estrogens and progestins and, as such, must be considered as having different actions and metabolism from the naturally occurring substances. Oral contraceptives contain one of two synthetic estrogens, both modifications of the naturally occuring estradiol 17-beta molecule. Attaching an ethinyl group to the 17 position of the estradiol molecule results in ethinyl estradiol, a compound which, in contrast to estradiol, is effective when administered orally. The 3-methyl ether of ethinyl estradiol is mestranol, also effective orally (Fig. 1). As the only hormone given, 80 μg of mestranol or 50 μg of ethinyl estradiol daily are sufficient to inhibit ovulation by hypothalmic suppression. In most contraceptive pills, these estrogens are combined with a progestin, which itself inhibits ovulation by suppressing the mid-cycle LH surge, giving an added safety factor in terms of effectiveness. A number of side effects have been attributed to the estrogenic component, making it advisable to reduce the estrogen content to the extent possible without trading off for other side effects or for reduced effectiveness.

A similar ethinyl substitution in the testosterone molecule results in the production of ethisterone, which is also orally active. Removal of the 19 carbon of ethisterone results in a group of compounds known as 19-nortestosterones, which have progestational activity. The prototype of these compounds is norethindrone (Fig. 2). Related compounds vary in their biologic properties in experimental situations (Fig. 3). A number of combinations of the estrogens and progestins are marketed for use as oral contraceptives. Most are given in a combined form but some are given sequentially. Newer pills contain only low-dose progestins given continuously (Table I). Pills differ in type and dosage of progestin and estrogen. Because of differences between progestins, there may be additional estrogenic, antiestrogenic, or progestational effects. Knowledge of such potential additive or antagonistic effects is important in choosing type of pills, and particularly important in evaluating side effects, in order to change, when necessary, to a better tolerated pill. Although an attempt should be made to initiate therapy based upon a rational analysis of the content of the pills, it is unknown whether the quantitated metabolism and action of the hormones is similar between patients, and one cannot predict their effects based entirely upon dosage levels. Hence arbitrary decisions must be made regarding type and dosage of hormones, with subsequent alterations as dictated by patient response.

From the Department of Obstetrics and Gynecology, College of Medicine and Dentistry of New Jersey.

Reprint requests: Alvin Langer, M.D., 65 Bergen St., Newark, New Jersey 07107.

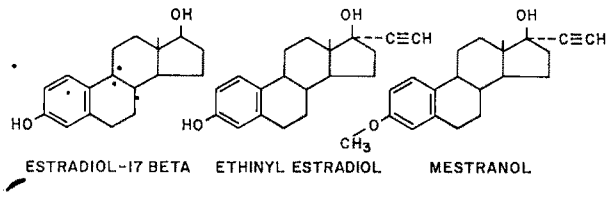


Fig. 1. Structures of estradiol and synthetic estrogens.

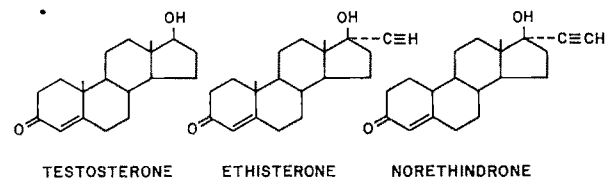


Fig. 2. Relationship of synthetic progestins to testosterone.

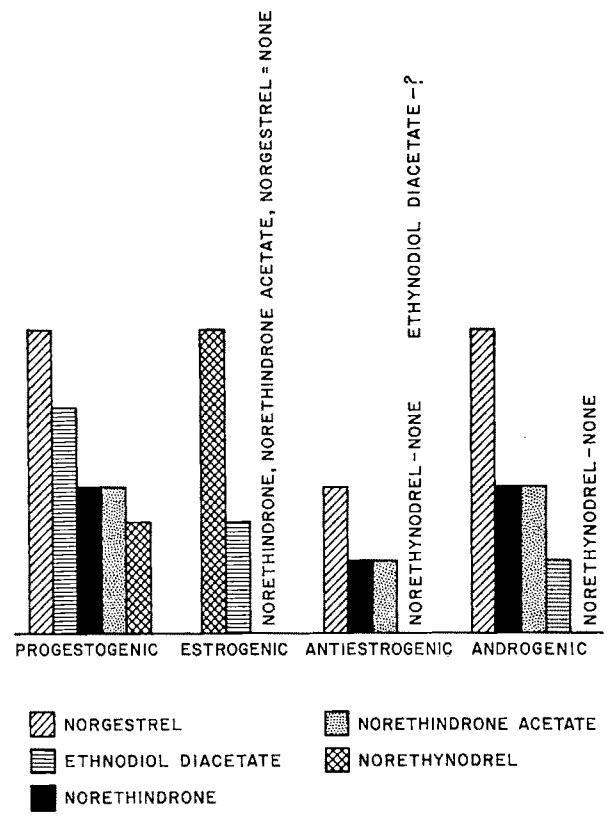


Fig. 3. Biologic effects of synthetic progestins.

Complications and side effects

A number of problems have been attributed to oral contraceptives. Some are hazardous or life threatening. Others, although not serious, are sufficiently annoying to the patient and her family to preclude the use of the medication at fault or cause ineffective use.

The increased incidence of thromboembolic disease is one of the more worrisome complications, even though such incidence is less than that during pregnancy or following delivery. Oral contraceptives effect physiologic changes which explain the increase in incidence of thromboembolism. During the first cycle of treatment, there is a consistent increase in platelet aggregation and, by the end of the third cycle, there is a consistent rise in factors VII and X. Also, there are less consistent increases in fibrinogen, factor VIII, and factor IX, and reductions in factor III (antithrombin) and fibrinolysin.[1] These changes in coagulability are specifically due to the estrogen component and are not found in women taking progestin-only pills. In addition, in women dying of thromboembolic disease while on oral contraceptives, histologic examinations have shown structural changes in blood vessels, with thrombi overlying these changes. Such changes have involved proliferation of the endothelium and thickening of the intima in small vessels. These may be demonstrated even without an overlying thrombus, indicating that the vascular disease antedates the formation of the thrombus.[2] The 1970 report of Inman and associates[3] is startling in relating the incidence of thromboembolic disease to the dosage of estrogen given. A dose of 50 μg seems to be the upper limit beyond which the risk increases, and empirically the dose of either estrogen should be limited to that amount unless specific indications for increased dosage exist.

Other factors possibly etiologic in vascular disease are related to these synthetic hormones. Women taking oral contraceptives have a slight but statistically significant rise in serum lipids, with an increase in low-density lipoproteins, the type made in the liver, and found elevated in type IV hyperlipidemia. Serum lipoproteins increase with estrogen dosage, but the effect is somewhat opposed by nortestosterone derivatives. Progestins, however, cause an increase in cholesterol. The end result is a rise in both classes of lipids. While the increase is usually small enough that the levels remain within the normal range, one must be concerned about the possible long-range effects of such elevations. At this time such effects remain unknown.

Oral contraceptives may be responsible for abnormalities in glucose tolerance tests. Estrogens alone, even in unusually high doses, are not capable of causing deterioration in glucose tolerance.[4] However, nortestosterone derivatives may effect deterioration when given alone in sufficiently high doses, an effect potentiated by estrogen. This potentiating effect of estrogen is not dose related.

Women using oral contraceptives occasionally develop marked hypertension. The reported incidence

Table I. Hormonal composition of currently used oral contraceptives (dose in milligrams)

Name	*Estrogen*		*Progestin*					
	Ethinyl estradiol	*Mestranol*	*Norethynodrel*	*Norethindrone*	*Norethindrone acetate*	*Ethynodiol diacetate*	*Norgestrel*	*Dimethisterone*
Combined:								
Enovid 10 mg.		0.150	9.85					
Enovid 5 mg.		0.075	5					
Enovid E		0.100	2.5					
Ovulen		0.100				1		
Demulen	0.050					1		
Ortho Novum 2 mg. and Norinyl 2 mg.		0.100		2				
Ortho Novum 1/80 and Norinyl 1 + 80		0.080		1				
Ortho Novum 1/50 and Norinyl 1 + 50		0.050		1				
Norlestrin 2.5 mg.	0.050				2.5			
Norlestrin 1 mg. and Zorane 1/50	0.050				1			
Zorane 1.5/30	0.030				1.5			
Zorane 1/20 and Loestrin 1/20	0.020				1			
Ovral	0.050						0.5	
Lo/Ovral	0.030						0.3	
Modicon and Brevicon	0.035			0.5				
Progestin only								
Micronor and Nor-QD				0.35				
Ovrette							0.075	
Sequential:								
Oracon	0.100							25
Ortho Novum SQ and Norquen	0.080			2				

has been as high as 15 per cent.[5] The hypertension is reversible after about 3 months of no medication but rapidly recurs if oral contraceptives are resumed. Although the mechanism of the rise in blood pressure is not entirely clear, it is thought to be due to an estrogen-induced increase in renin substrate (angiotensinogen). This results in an increase in angiotensin I and angiotensin II and ultimately in aldosterone. Susceptible women appear to be unable to implement the normal feedback mechanism, whereby the production of renin by the juxtaglomerular apparatus of the kidney is decreased by increasing levels of angiotensin.

Headaches are occasional complications of pills, seeming to be most frequent during the intervals between medication. Currently too little is known to relate the headaches to either hormone or its dosage, and there is no information to aid the physician in pill choice. Headaches, however, must be evaluated as to whether they are vascular or tension and whether they began after initiating oral contraceptives. Vascular headaches should be considered a contraindication to pill use.

The incidence of mental depression in women taking oral contraceptives has been reported as high as 6.6 per cent.[6] This depression appears to be related to estrogen-induced alterations of vitamin B_6 metabolism.

A number of minor but annoying side effects may occur in women on the pill. Engorgement and sensitivity of breasts is related to estrogen dosage. Occurrence of nausea and vomiting has been reported as high as 15 per cent and also appears to be related to the estrogen. Weight gain may appear in one of two forms. Cyclic changes are apparently due to fluid retention caused by estrogen, whereas persistent increase in weight is probably due to the anabolic effects of some of the androgenic progestins. Other androgen-related side effects include hirsuitism, acne, or alopecia. There are conflicting reports as to whether the incidence of monila vaginitis is increased in women on oral contraceptives. In a prospective evaluation, Spellacy and associates[7] found no increase. However, many physicians are of the impression that women on combined oral contraceptives seem especially susceptible to monilia vaginitis and that they may improve if taken off oral contraceptive or changed to a sequential pill, which causes increased vaginal cornification.

Contraceptives may influence the amount of menstrual bleeding. Some women are annoyed by spotting or breakthrough bleeding. The incidence appears to be higher on low-estrogen or no-estrogen

Table II. Contraindications to oral contraception

Absolute:
Present or past thromboembolic disease
Present or past cerebrovascular accident
Breast mass—before histologic diagnosis
Active liver disease
History of cholestatic jaundice during pregnancy
History of severe mental depression
Young patient—prior to cessation of growth
Poor motivation—inability to understand and follow directions
Vascular headaches
Relative:
Hypertension
Diabetes mellitus
Rheumatic heart disease
Puerperium
Family history of breast cancer
Severe varicose veins
Convulsive disorders
Oligo- or amenorrhea

pills, and may be relieved by increasing the estrogen content. On the other hand, some women are bothered by scanty flow or by amenorrhea. These are apparently related either to low estrogen dosage or high progestin dosage, and can be treated by changing the appropriate component in the pills.

Choice of pills

The physician has clinical methods of evaluating the patient in the choice of the correct contraceptive. An accurate and detailed history and a thorough physical examination are mandatory to proper selection. Contraindications must be ruled out before the pill is prescribed (Table II).

In beginning therapy in a patient with no specific contraindications and nothing leading to the expectation of specific problems, we aim at an optimal effective dosage giving minimal risk and side effects. Since risks appear to be increased as estrogen dosage is increased above 50 μg, but breakthrough bleeding is more likely to occur at lower doses, we begin with 50 μg of either mestranol or ethinyl estradiol. In prescribing the progestin, we choose the smallest possible dose available. In general, we have no preference of specific progestins, but avoid the more androgenic types, especially in patients showing androgenic effects, such as hirsuitism, prior to therapy. In patients showing hyperresponsiveness to their endogenous estrogens, by such symptoms as heavy periods, premenstrual breast soreness, large breasts, or cyclic weight gain, the more androgenic progestins are used, but the more estrogenic are not.

The patient being treated with oral contraceptives is seen on a regular basis, at least semiannually. Each examination includes measurement of weight and blood pressure and examination of breasts and pelvic organs. In addition, a probing, thorough questioning about side effects is done. When indicated by severity or type of symptoms, the pills are discontinued or the hormonal components of the pills are altered. Occasionally the patient's pattern of taking the pills is corrected. For example, in the patient complaining of nausea, care is taken to ascertain that the patient is taking the medication on a full stomach. Heavy menstrual bleeding is treated by increasing the progestin dosage or by decreasing the estrogen dosage, and scanty bleeding or amenorrhea is treated in the opposite manner. Intermenstrual bleeding is treated by increasing estrogen dosage, providing organic disease is excluded. Patients complaining of depression are treated with pyridoxine hydrochloride, 20 mg. twice a day. If this is ineffective, the pills are discontinued. Weight gain of an amount which is bothersome to the patient is treated by reducing either estrogen or progestin, depending upon the cyclicity of the gain. The appearance of vascular headaches, thromboembolic phenomena, severe leg cramps, visual disturbances, or hypertension are considered indications to permanently discontinue the pills. Yearly blood counts and urinalyses are performed, and anemia is appropriately evaluated and treated. Glucose tolerance tests are not routinely performed before or during treatment, but are ordered in the event of a suggestive history or glycosuria appearing at any time.

Neither sequentials, "low-dose" estrogen (less than 50 μg), nor progestin-only minipills are routinely chosen as the initial therapy, because of concern about decreased effectiveness and/or increased incidence of side effects. Patients with persistent monilia vaginitis, in spite of adequate treatment, on combined pills, are switched to sequential therapy or given another treatment. The low-estrogen pills are used only in patients expressing concern about estrogen-related side effects and motivated and intelligent enough to cope with the increased incidence of breakthrough bleeding or amenorrhea with these pills, and the knowledge that there is possibly less of a safety from unwanted pregnancies if pills are unintentionally omitted. The progestin-only minipills are used only in patients with specific contraindications to estrogen and who find other methods of contraception unacceptable. Their increased pregnancy rates and increased incidence of annoying side effects are considered sufficient reason to preclude their usage by all but a few patients.

The problem of forgotten pills is managed according to the number of days involved. If one or two pills are

omitted, they are made up for by doubling the dose for the following 1 or 2 days. If three or more consecutive pills are missed, their usage for that cycle is stopped, allowing withdrawal bleeding to occur, and pills are resumed 1 week after the last pill was taken. In any event of missed pills, a mechanical method of contraception is recommended until the next withdrawal bleeding. Patients who repetitively omit pills are usually advised to switch to a method requiring less active participation on their part, such as the intrauterine device or surgical sterilization.

If neither pill-related symptoms nor abnormal physical findings occur, we do not place a time limit on pill usage. In our opinion, the menstrual pattern occurring after stopping the pills temporarily does not necessarily indicate the pattern that will occur after further hormonal contraception. While we realize the potential of post-pill amenorrhea, we feel that, in view of the necessity of initiating another type of contraception during the time off pills, the nuisance resulting from attempted early diagnosis more than overcomes any possible benefits.

It should be recognized that oral contraceptives contain potent pharmacologic agents capable of long-range disturbances in physiology after stopping therapy as well as serious or life-threatening complications during therapy. As with other medications, potential benefits should outweigh the risks, and a thorough evaluation before therapy and close follow-up during therapy are absolute necessities.

REFERENCES

1. Poller, L., Tabiowo, A., and Thompson, J. M.: Effects of low-dose oral contraceptives on blood coagulation, Br. Med. J. **3:** 218, 1968.
2. Masi, A. T., and Dugdale, M.: Cerebrovascular diseases associated with the use of oral contraceptives, Ann. Intern. Med. **72:** 111, 1970.
3. Inman, W. H. W., Vessey, M. P., Westerholm, B., and Engelund, A.: Thromboembolic disease and the steroidal content of oral contraceptives, Br. Med. J. **2:** 203, 1970.
4. Spellacy, W. N., Buhi, W. C., and Birk, S. A.: The effect of estrogens on carbohydrate metabolism: Glucose, insulin, and growth hormone studies on one hundred and seventy-one women ingesting Premarin, mestranol and ethinyl estradiol for six months, AM. J. OBSTET. GYNECOL. **114:** 378, 1972.
5. Saruta, T., Saade, G. A., and Kaplan, N. M.: A possible mechanism for hypertension induced by oral contraceptives, Arch. Intern. Med. **126:** 621, 1970.
6. Adams, P. W., Rose, D. P., Folkard, J., Wynn, V., Seed, M., and Strong, R.: Effect of pyridoxine hydrochloride (vitamin B_6) upon depression associated with oral contraception, Lancet **1:** 897, 1973.
7. Spellacy, W. N., Zaias, N., Buhi, W. C., and Birk, S. A.: Vaginal yeast growth and contraception practices, Obstet. Gynecol. **38:** 343, 1971.

What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.

GYNECOLOGY

Cul-de-sac isolates from patients with endometritis-salpingitis-peritonitis and gonococcal endocervicitis

GILLES R. G. MONIF, M.D.
SUSAN L. WELKOS
HERMAN BAER, M.D.
ROBERT J. THOMPSON, M.D.
Jacksonville and Gainesville, Florida

Neisseria gonorrhoeae *was cultured from the cul-de-sac in 11 of 17 patients with bacteriologically documented gonococcal endometritis-salpingitis and identified by Gram stain in one other instance. In five,* N. gonorrhoeae *was the only isolate. In six other patients, the presence of other aerobic (two) and anaerobic bacteria (three), as well as* N. gonorrhoeae, *was documented. In the remaining six patients, only aerobic and anaerobic organisms were isolated. The data are interpreted as supporting the concept of anaerobic superinfections following initial infection with* N. gonorrhoeae *late in the course of this disease entity.*

RECENT BACTERIOLOGIC studies of patients with endometritis/salpingitis/peritonitis have demonstrated, in the majority of instances, the presence in the cul-de-sac of bacteria other than *Neisseria gonorrhoeae.*[1, 2] The relative rarity with which *Neisseria gonorrhoeae* is isolated from the cul-de-sac, despite recovery from the endocervix, not only has engendered a concept of polymicrobial etiology for pelvic inflammatory disease but also has led a leading West Coast anaerobiologist to frankly question the etiologic role of *Neisseria gonorrhoeae* in this entity.[3]

This paper reports the bacteriologic observations derived by culdocentesis on 17 patients with gonococcal endocervicitis/endometritis from whom one or more bacteria were isolated.

From the Laboratory of Infectious Diseases/Anaerobic Laboratory, the Departments of Obstetrics and Gynecology and Microbiology, University of Florida College of Medicine, and the Department of Obstetrics and Gynecology, University Hospital.

Supported by a grant from Pfizer Lab., Div. Chas. Pfizer & Co., Inc., 235 E. 42nd St., New York, New York 10017.

Received for publication March 16, 1976.

Revised June 14, 1976.

Accepted July 6, 1976.

Reprint requests: Dr. Gilles R. G. Monif, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida 32610.

Materials and methods

Patient population. The study patients were drawn from women presenting for medical care at the Shands Teaching Hospital in Gainesville, Florida, and the University Hospital in Jacksonville, Florida, between November, 1974, and March, 1976. Criteria for inclusion in this study were the presence of: (1) local and systemic signs and symptoms consistant with endometritis and salpingitis, (2) recoverability of *Neisseria gonorrhoeae* from the endocervix and/or cul-de-sac, (3) signs of peritoneal irritation, and (4) a culdocentesis specimen which yielded one or more bacterial isolates.

Table I. Patients with *Neisseria gonorrhoeae* isolated from either the endocervix or cul-de-sac in whom culdocentesis specimens yielded bacterial isolates

Case	*Smear (endocervix)*	*Thayer-Martin or Lester-Martin agar (endocervix)*	*Culdocentesis*
1	Positive	Positive	*Neisseria gonorrhoeae*
2	Negative	Positive	*Neisseria gonorrhoeae*
3	Positive	Positive	*Neisseria gonorrhoeae*
4	Positive	Positive	*Neisseria gonorrhoeae*
5	Positive	Positive	*Neisseria gonorrhoeae*
6	Positive	Positive	*Neisseria gonorrhoeae,* group B beta-hemolytic streptococci
7	Positive	Positive	*Neisseria gonorrhoeae,* alpha streptococci, not group D; staphylococcus, coagulase negative
8	Positive	Positive	*Neisseria gonorrhoeae,* microaerophilic corynebacterium; Peptostreptococcus spp.; Bacteroides spp.; Veillonella spp.
9	Positive	Positive	*Neisseria gonorrhoeae,* nonhemolytic streptococci, not group D; staphylococcus, coagulase negative; Bacteroides spp.
10	Positive	Positive	*Neisseria gonorrhoeae;* Peptostreptococcus spp.; Bacteroides spp. No. 1; Bacteroides spp. No. 2; enterococci
11	Negative	Negative	*Neisseria gonorrhoeae; Haemophilus vaginalis; Peptococcus prevotii; Eubacterium aerofaciens; Bacteroides fragilis*
12	Negative	Positive	Smear showed gram-negative diplococci; Peptococcus spp.
13	Negative	Positive	*Escherichia coli; Bifidobacterium longum, adolescents,* and *infants; Bacteroides fragilis;* ss. *vulgatis;* Bacteroides spp.; *Eubacterium tenue*
14	Negative	Positive	Nonhemolytic streptococci, not group D
15	Negative	Positive	Peptococci
16	Negative	Positive	*Serratia marcescens;* enterococci; *Peptostreptococcus anaerobius*
17	Negative	Positive	Enterococci; staphylococcus, coagulase negative; Peptostreptococcus spp.; *Bacteroides fragilis; Clostridium malenominatum*

The above study grouping does not delineate the incidence of isolation of *N. gonorrhoeae* from the cul-de-sac. Eleven patients with documented gonococcal endocervicitis/endometritis were concomitantly studied, and in each a valid sampling containing a significant number of white blood cells was obtained from the cul-de-sac from which no bacteria were isolated.

Bacteriologic techniques. At the time of the initial examination, Gram stains were made of the endocervix and culdocentesis fluid. If deemed positive, the smear was saved and reviewed independently by a second observer (G. R. G. M.) to confirm the validity of the original observation. An endocervical culture was obtained with a sterile cotton applicator and plated directly on Thayer-Martin agar (Shands Teaching Hospital) or Lester-Martin agar (University Hospital). Culdocentesis was performed under direct visualization with a No. 18 gauge needle and syringe through a surgical field which had been dried with a cotton drumstick and washed with povidone-iodine* solution. One to four milliliters of the fluid obtained by culdocentesis was injected into two Anaport† bottles. One of the Anaport bottles was then sent to the hospital Microbiology Laboratory, and the other was forwarded to the Anaerobic Laboratory of the Departments of Obstetrics and Gynecology and Microbiology. The specimen received by the hospital laboratory was immediately subcultured for *N. gonorrhoeae*, whereas that forwarded to the anaerobic laboratory was held for at least 24 to 48 hours or more at room temperature prior to the establishment of subcultures.

Processing of cul-de-sac specimens. The cul-de-sac specimens in the Anaport transport bottles were passed into an anaerobic chamber–glove box* immediately upon receipt. The specimen was retrieved with a needle and syringe and plated on various selective media listed below. In addition, thioglycollate broth containing hemin (5 μg per milliliter) and menadione (0.5 μg per milliliter) was inoculated. The plating media for anaerobic culture included: Columbia agar base containing 5 per cent sheep blood, cysteine hydrochloride (0.5 Gm. per liter), palladium chloride (0.33 Gm. per liter), and vitamin K–hemin solution (ABAP); ABAP supplemented with vancomycin hydrochloride (7.5 mg. per liter) and kanamycin sulfate (75 mg. per liter) and containing laked sheep blood; lecithin-lactose agar (Ellner reference); Veillonella agar†; and Rogosa

*Betadine, Purdue Frederick Co., 99-101 Saw Mill River Rd., Yonkers, New York 10701.

†Anaport, Scott Laboratories, Inc., Fiskeville, Rhode Island 02823.

*Coy Manufacturing Co.

†Difco Labs., 920 Henry St., Detroit, Michigan 48201.

Table II. Comparison of bacterial isolation in patients with gonococcal endometritis/salpingitis/peritonitis from the recent literature

Series	*Incidence of recovery of* N. gonorrhoeae *from the cul-de-sac in patients with gonococcal endometritis/salpingitis/peritonitis*	*Percentage with* N. gonorrhoeae *as the sole isolate from the cul-de-sac*	*Percentage with* N. gonorrhoeae *aerobic/facultative anaerobic bacteria*	*Percentage with* N. gonorrhoeae *and facultative/obligatory anaerobes*	*Anaerobic dominance*
Chow and associates[1]	1/13 (8%)	N.S.	N.S.	N.S.	N.S.
Eschenbach and colleagues[2]	7/21 (33%)*	6/21 (23%)*	1/21 (5%)	0/21 (0%)	5/21 (24%)
This study	11/17 (65%)*	5/17 (29%)	3/17 (18%)	1/21 (5%) 3/17 (18%) 6/17 (35%)	6/17 (35%)*

N.S. = Not stated.

*In one additional case not included in these figures, Gram stain of the culdocentesis exudate revealed gram-negative diplococci.

selective Lactobacillus agar.* All media for anaerobic culture were placed in the reducing conditions of the glove box or an anaerobic jar (Baltimore Biological Laboratory) containing a Gas-Pak generator envelope for at least 24 hours prior to use. All inoculated anaerobic culture plates were placed in an anaerobic jar (Baltimore Biological Laboratory) and incubated at 37° C.

In addition, the cul-de-sac specimens were cultured for anaerobic organisms on the following media: 5 per cent sheep blood agar (BAP), MacConkey agar,* Pfizer selective Enterococcus medium,† and chocolate agar or Thayer-Martin media. The inoculated media were incubated in air containing carbon dioxide at 37° C.

An aliquot of specimen in the transport container was stained by the Gram method to directly determine the predominant morphologic types of organisms present.

Identification of strains. Aerobic isolates were subcultured and identified by a standard classification scheme.[3] Isolated colonies from anaerobic plates were subcultured for identification beginning 48 hours after inoculation. The primary plates were re-examined at intervals up to 10 days after inoculation. Colonies were assigned to ABAP for purity, to peptone yeast extract glucose (PYG) broth, and to BAP for aerotolerance testing. The anaerobic isolates were identified following the methods of Virginia Polytechnic Institute Anaerobic Laboratory.[4] Morphologic, cultural, and biochemical properties were employed. Carbohydrate fermentation reactions were read with a pH meter. In addition, gas-liquid chromatography was performed on extracted PYG broth cultures to detect fatty acid production. A gas chromatograph having a thermal conductivity detector* was used to detect fatty acid end products of metabolism.

*Difco Labs.

†Pfizer Lab., Div. Chas. Pfizer & Co., Inc.

Results

Of the 17 patients with bacteriologically documented gonococcal infection, *Neisseria gonorrhoeae* was cultured from the cul-de-sac in 11 cases and identified by Gram stain in one additional instance. *N. gonorrhoeae* was the sole isolate achieved in five patients. From Cases 6 and 7 aerobic bacteria were concomitantly recovered. In four other cases (8 to 11), culdocentesis yielded, in addition to *N. gonorrhoeae*, multiple anaerobic organisms (Table I). In the remaining six cases (12 to 17), aerobic and anaerobic organisms were isolated; however, in one instance gram-negative intracellular diplococci were present in small numbers on the Gram stain of the culdocentesis exudate.

If one looks at the observation derived from analysis of the Gram stain of the endocervix, there is a cleavage in the data: Intracellular gram-negative diplococci were present in 10 of 11 smears where *N. gonorrhoeae* alone or together with aerobic/anaerobic bacteria was isolated in contrast to the failure of their demonstration when *N. gonorrhoeae* was absent from the culdocentesis fluid. In four of six of these cases, the quantity of *N. gonorrhoeae* recovered by endocervical culturing was numerically small (in one instance, five colonies were isolated).

Comment

In 1897, Menge reported the isolation of *N. gonorrhoeae* from 21.7 per cent of the cases of purulent salpingitis. Subsequent figures have ranged from 18 to 22 per cent.[5] In 1921, Curtis[6] presented a 9.8 per cent

*Dohrmann Instruments Co., Infotronics, Inc., 7800 Westglen Dr., Houston, Texas 77042.

figure from a study of 192 specimens. He came to the conclusion that *N. gonorrhoeae* persisted in the Fallopian tubes for a comparatively short period of time and that the tubes were totally sterile 10 to 14 days after the acute symptoms had abated. The major point of Curtis' study was that the tubes were not a site of persistent infection and that subsequent episodes of acute pelvic inflammatory disease involving the Fallopian tubes represented true reinfection from the lower genital tract. Hundley and associates[5] subsequently carried out a surgical-bacteriologic survey in which they isolated the gonococcus in 41.25 per cent of cases from the urethra and cervix and in 6.25 per cent from the Fallopian tube. Again, every case of gonococcal tubal infection was associated with infection of the cervix and urethra, corroborating the position of Curtis.[6] The probability that *N. gonorrhoeae* is involved in the subsequent pathogenesis of the ensuing salpingitis and peritonitis is suggested by the studies of Studdiford and colleagues.[7] They sampled tubal exudate and Fallopian tube fragments from 24 consecutive cases. While unable to recover the gonococcus from the tubal exudate, they did isolate the organism from 16 of 24 tissue specimens. What the data of the 1970's are focusing on is the mechanism by which polymicrobial infection of the Fallopian tubes and peritoneal cavity develops in cases of gonococcal endocervicitis and presumably endometritis.

There is no question about the validity of the concept of polymicrobial infection of acute pelvic inflammatory disease (as opposed to polymicrobial etiology) late in the course of gonococcal endometritis-salpingitis when peritonitis is present. In many instances, particularly where there is underlying pre-existing destruction of the Fallopian tube architecture, it is difficult to incriminate *Neisseria gonorrhoeae* as the causative pathogen. However, when dealing exclusively with disease from which *Neisseria gonorrhoeae* can be recovered, the polymicrobial infection which occurs late in the course of infection may be the consequence of a different process. From our data, an alternate hypothesis to that of polymicrobial etiology, namely, anaerobic superinfection with nonrecovery and probable elimination of *N. gonorrhoeae*, is suggested. *N. gonorrhoeae* was the sole bacterium recovered from the cul-de-sac in five patients. This pattern of recovery was identical to that in six of seven patients of Eschenbach and co-workers[2] (Table II). From their remaining patients, an aerobe, as well as *N. gonorrhoeae*, was isolated. From Cases 6 and 7, *N. gonorrhoeae*, in conjunction with aerobic/facultative anaerobic bacteria, was isolated (comparable to the findings in the remaining patients of the series of Eschenbach and co-workers). The critical distinction between the data presented in these two series and our data is the finding in four patients in whom culdocentesis yielded, in addition to *N. gonorrhoeae*, multiple aerobic/anaerobic bacteria (Table II). In these situations, the presence of aerobic/facultative anaerobes with obligatory anaerobes argues against an end-stage anaerobic environment. This pattern of cul-de-sac bacterial recovery in conjunction with the progressive difficulty in identifying gram-negative intracellular diplococci when mixed infection occurs is suggestive of progressive anaerobic superinfection and may forge the critical link between the data of Eschenbach and co-workers and our data.

REFERENCES

1. Chow, A. W., Malkasian, K. L., Marshall, J. R., and Guze, L. B.: The bacteriology of acute pelvic inflammatory disease. Value of cul-de-sac cultures and relative importance of gonococcal and other aerobic or anaerobic bacteria, Am. J. Obstet. Gynecol. **123:** 876, 1975.
2. Eschenbach, D. A., Buchanan, T. M., Pollack, H. M., Forsyth, P. S., Alexander, E. R., Lim, J. S., Wang, S. P., Wentworth, B. B., McCormack, W. M., and Holmes, K. K.: Polymicrobial etiology of acute pelvic inflammatory disease, N. Engl. J. Med. **293:** 166, 1975.
3. Lennette, E. H., Spaulding, E. H., and Truant, J. P.: Manual of Clinical Microbiology, ed. 2, Washington, D. C., 1974, American Society for Microbiology.
4. Holdeman, L. V., and Moore, W. E. C.: Anaerobe Laboratory Manual, Blacksburg, Virginia, 1972, Virginia Polytechnic Institute.
5. Hundley, J. M., Jr., Diehl, W. K., and Baggot, J. W.: Bacteriological studies on salpingitis with special reference to gonococcal viability, Am. J. Obstet. Gynecol. **60:** 977, 1950.
6. Curtis, A. H.: Bacteriology and pathology of Fallopian tubes removed at operation, Surg. Gynecol. Obstet. **33:** 621, 1921.
7. Studdiford, W. E., Casper, W. A., and Scadron, E. N.: The persistence of gonococcal infection in the adexa, Surg. Gynecol. Obstet. **67:** 176, 1938.
8. Thayer, J. D., and Garson, W.: The gonococcus, *in* Dubos, R., and Hirsch, J. G., editors: Bacterial and Mycotic Infections of Man, ed. 4, Philadelphia, 1965, J. B. Lippincott Company, pp. 453-454.

The effect of L-dopa and chlorpromazine on prolactin and growth hormone secretion in normal women

H. LEBLANC*

S. S. C. YEN

La Jolla, California

The time course of simultaneous changes in prolactin (PRL) and growth hormone secretion in response to a single dose of L-dopa and chlorpromazine was determined in normal women. L-Dopa induced greater, but shorter (30 minutes), growth hormone release than concomitant suppression of PRL secretion. The PRL peak following chlorpromazine occurred at the same time as the nadir of PRL after L-dopa (3.5 hours). The quantity of PRL release inhibited by L-dopa equaled the amount of PRL secretion during the period of rebound, suggesting L-dopa inhibits PRL release, but not synthesis, by the pituitary.

CHLORPROMAZINE (CPZ) and L-dopa have been used clinically in the assessment of the hypothalamic function in the regulation of prolactin (PRL) and growth hormone (GH) secretions by the adenohypophysis.[1–7] Both drugs presumably act directly on the hypothalamus and affect central nervous system catecholaminergic mechanisms.[8–10] L-Dopa, a precursor of dopamine, induces a transient depression of plasma PRL levels[1–4] and a rise in plasma GH secretion.[5, 6] CPZ, a phenothiazine which blocks dopamine uptake into storage granules, promotes PRL secretion[3, 4] and suppresses GH release in the presence of insulin-induced hypoglycemia.[7] However, the precise time course of acute effects of L-dopa and CPZ administration on concomitant changes in circulating levels of PRL and GH in normal women has not been defined. This report describes the results of such a study.

From the Department of Reproductive Medicine, School of Medicine, University of California, San Diego.

Supported by Rockefeller Foundation Grant RF 75029. A portion of the patient studies was performed in the Clinical Research Center supported by National Institutes of Health Research Grant RR00827.

Received for publication November 14, 1975.

Accepted February 3, 1976.

Reprint requests: Dr. S. S. C. Yen, University of California, San Diego, Department of Obstetrics and Gynecology, University Hospital of San Diego County, P. O. Box 3548, 225 W. Dickinson St., San Diego, California 92103.

**Former Research Fellow in Reproductive Endocrinology. Present Address: Hopital Maisonneuve, Lab d'Endocrinologie, 5415 BD L'Assomption, Montreal, Quebec, Canada.*

Material and methods

Six normal women, ages 25 to 29, were studied during the early follicular phase of the menstrual cycle (Days 3 to 5). All subjects reported to the Ambulatory Clinical Research Unit between 0730 and 0800 after an overnight fast and were placed at bed rest, but none of them slept during the test. They were free from medical illness and had not received any kind of medication for at least three months prior to the study. Three women receiving 25 mg. of CPZ* intramuscularly and to the other three, 500 mg. of L-dopa† was administered orally. Two hours prior to the administration of the drug, a No. 18 gauge polyethylene cannula was placed in an antecubital vein for sampling and kept open with a slow drip of normal saline. Blood samples were collected every 15 minutes for one hour prior to and 10 hours after the administration of the drug. Breakfast was omitted, but all subjects had lunch at 1230 and dinner at 1745 hours.

GH and PRL concentrations were determined by radioimmunoassay methods previously described.[11, 12] The paired t test was used for statistical analyses.

Results

The effect of a single dose of CPZ (25 mg. intramuscularly) on serum prolactin levels is shown in Fig. 1. There was a slow rise in circulating PRL, and a maximum level (more than doubled) was reached at 3 hours and 30 minutes. Thereafter, PRL levels de-

*Thorazine, Smith Kline & French Labs., 1500 Spring Garden St., Philadelphia, Pennsylvania 19101.

†Larodopa, Roche Labs., Div. Hoffmann-La Roche Inc., Roche Park, Nutley, New Jersey 07110.

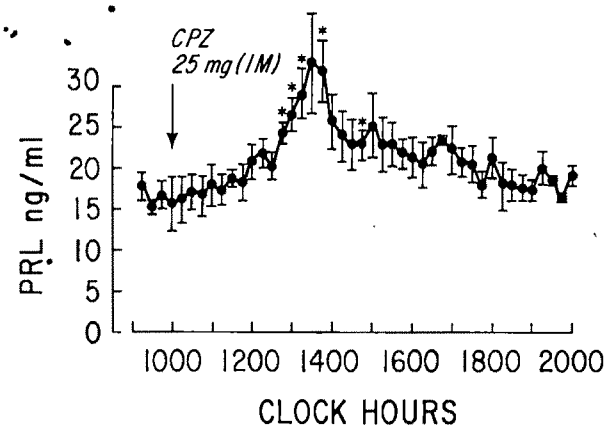


Fig. 1. Effect of 25 mg. of CPZ on PRL level (mean ± S.E.M.) in three normal women. * Indicates $p < 0.05$, significantly different when compared with pretreatment values.

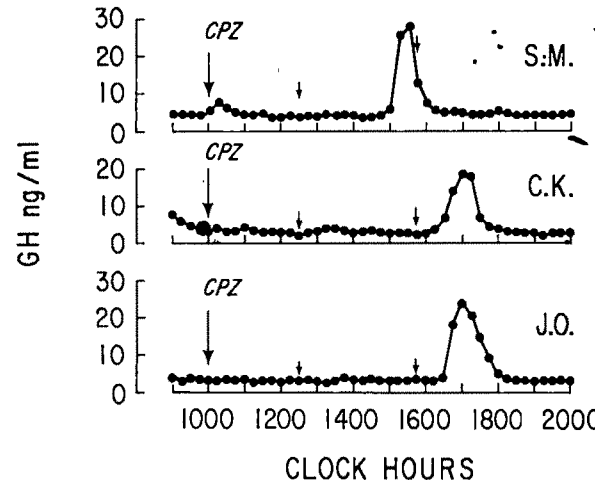


Fig. 2. Effect of 25 mg. of CPZ on GH levels in three women. Small arrows represent food intake.

creased slowly and returned to basal levels at 10 hours after the injection. There was no episodic GH release during the first five to seven hours following CPZ administration, but spontaneous episodic secretions were observed in all three subjects during the last three to five hours of observation (Fig. 2).

Fig. 3 shows the effect of 500 mg. of L-dopa on the simultaneous change in GH and prolactin levels. As expected, there was a prompt release of GH and a peak tenfold rise was reached within one hour. This was followed by a rapid decline toward basal levels which was maintained during the period of observation. The secretion of PRL was inhibited with a maximum decrease of 40 per cent occurring at three hours after the administration of L-dopa. This was followed by a rapid return to the basal level and a rebound in PRL release which was sustained for a period of three hours. The area under the curve for PRL during the period of suppression was equal to that calculated during the period of rebound secretion (Fig. 3).

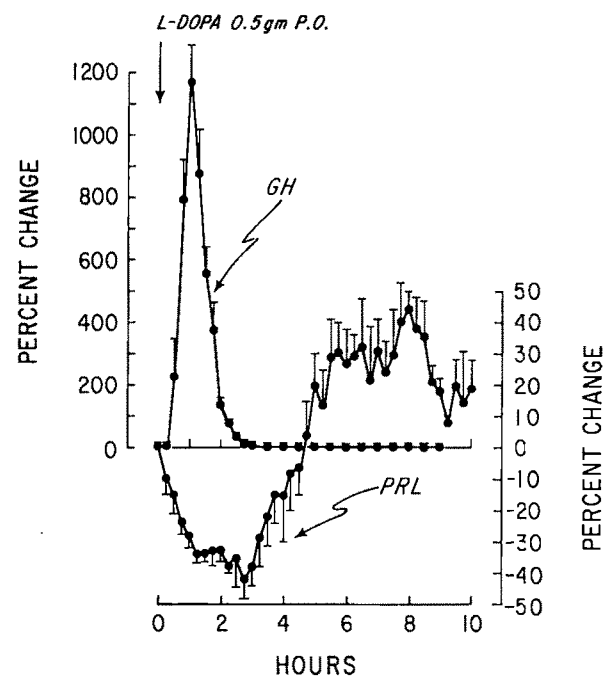


Fig. 3. Per cent change (mean ± S.E.M.) and the time course in GH and PRL levels in response to 500 mg. of L-dopa in three normal women.

Comment

The present study confirms the effects of CPZ and L-dopa on the secretion of PRL and GH previously reported.[1-7] Using frequent samplings and a longer period of observation, our findings have afforded additional information concerning the time course of these actions (Figs. 1 to 3). Thus, the PRL peak and nadir following CPZ and L-dopa, respectively, occurred approximately at the same time (3 to 4 hours). In response to L-dopa, the release of GH appears to follow a more rapid but briefer time course than that of the PRL suppression (1 hour versus 3 hours). It is possible that the spontaneous episodic GH release sometimes seen during the morning hours[13, 14] may have been inhibited by CPZ (Fig. 2). This possibility is consistent with the findings of an impairment of hypoglycemia-induced GH release in subjects receiving long-term CPZ treatment.[7]

A rebound in PRL secretion following a period of suppression by L-dopa was clearly evident (Fig. 3). It is of interest that the amount of PRL secretion during the period of rebound equaled the amount of PRL inhib-

ited, suggesting that L-dopa and its subsequent conversion to dopamine had blocked the pituitary secretion but not the synthesis of PRL. This is in accord with the finding of MacLeod and Lehmeyer[15] that incubation of rat pituitaries with dopamine inhibits the in vitro secretion but not the synthesis of PRL.

We wish to thank J. Aurand, B. King, P. Malcom, M. Sigel, and T. Vargo for their technical assistance.

REFERENCES

1. Frantz, A. G., Suh, H. K., and Noel, G. L.: Effects of L-dopa on prolactin secretion in humans, *in* Usdin, E., and Snyder, S. H., editors: Frontiers in Catecholamine Research, Oxford, 1973, Pergamon Press, Inc., p. 843.
2. Noel, G. L., Suh, H. K., and Frantz, A. G.: L-Dopa suppression of TRH-stimulated prolactin release in man, J. Clin. Endocrinol. Metab. **36:** 1255, 1973.
3. Friesen, H., Guyda, H., Hwang, P., Tyson, J. C., and Barbeau, A.: Functional evaluation of prolactin secretion: A guide to therapy, J. Clin. Invest. **51:** 706, 1972.
4. Kleinberg, D. L., Noel, G. L., and Frantz, A. G.: Chlorpromazine stimulation and L-dopa suppression of plasma prolactin in man, J. Clin. Endocrinol. Metab. **33:** 873, 1971.
5. Boyd, A. E., Lebovitz, H. E., and Pfeiffer, J. B.: Stimulation of human-growth-hormone secretion by L-dopa, N. Engl. J. Med. **283:** 1425, 1970.
6. Hayek, A., and Crawford, J. D.: L-Dopa and pituitary hormone secretion, J. Clin. Endocrinol. Metab. **34:** 764, 1972.
7. Sherman, L., Kim, S., Benjamin, F., and Kolodny, H. D.: Effect of chlorpromazine on serum growth-hormone concentration in man, N. Engl. J. Med. **284:** 72, 1971.
8. DeWierd, D.: Chlorpromazine and endocrine function, Pharmacol. Rev. **19:** 251, 1967.
9. Kamberi, I. A., Mical, R. S., and Porter, J. C.: Effect of anterior pituitary perfusion and intraventricular injection of catecholamines on prolactin release, Endocrinology **88:** 1012, 1971.
10. Birge, C. A., Jacobs, L. S., Hammer, C. A., and Daughaday, W. H.: Catecholamine inhibition of prolactin secretion by isolated rat adenohypophysis, Endocrinology **86:** 120, 1970.
11. Yen, S. S. C., Samaan, N., and Pearson, O. P.: Growth hormone levels in pregnancy, J. Clin. Endocrinol. Metab. **27:** 1341, 1967.
12. Ehara, Y., Siler, T., VandenBerg, G., Sinha, Y. N., and Yen, S. S. C.: Circulating prolactin levels during the menstrual cycle: Episodic release and diurnal variation, AM. J. OBSTET. GYNECOL. **117:** 962, 1973.
13. Goldsmith, S. J., and Glick, S. M.: Rhythmicity of human growth hormone secretion, Mt. Sinai J. Med. N. Y. **37:** 501, 1970.
14. Parker, D. C., and Rossman, L. G.: Physiology of human growth hormone release in sleep, Proceedings of the Fourth International Congress of Endocrinology, Washington, D. C., Amsterdam, 1973, Excerpta Medica Foundation, p. 655.
15. MacLeod, L. M., and Lehmeyer, J. E.: Studies on the mechanism of the dopamine-medicated inhibition of prolactin secretion, Endocrinology **94:** 1077, 1974.

Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause

SEZER AKSEL, M.D.
DAVID W. SCHOMBERG, PH.D.
LEE TYREY, PH.D.
CHARLES B. HAMMOND, M.D.
Durham, North Carolina

Hormonal parameters of young women who developed vasomotor symptoms in the immediate postoperative period following castration are compared to those who remained asymptomatic. Only 37.5 per cent of 16 premenopausal women developed "hot flushes" after operation. Perimenopausal women with vasomotor symptoms and elevated follicle-stimulating hormone levels demonstrated normal luteinizing hormone and estrogen values preoperatively. There were no statistically significant differences in total serum estrogen, follicle-stimulating hormone, or luteinizing hormone concentrations between the group of patients with symptoms and the group without symptoms. The results of the study indicate that rising gonadotropin or declining estrogen values appear to have no direct correlation to the onset of vasomotor symptoms in the immediate postoperative period. Thus, the precise etiology of the "hot flush" remains to be elucidated.

VASOMOTOR SYMPTOMS frequently observed in women during the perimenopausal years have been commonly correlated with failing ovaries and a declining estrogen level. Vasomotor symptoms are also observed in young women who develop premature menopause spontaneously or following oophorectomy. There is considerable variation in the intensity and frequency of symptoms. Some patients become incapacitated with discomfort during this period while others never experience a single "hot flush." The present study was designed to evaluate vasomotor symptoms and the levels of total serum estrogen, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in premenopausal and perimenopausal patients who underwent surgical procedures including bilateral oophorectomy. These parameters were compared among patients who did and did not develop vasomotor symptoms in the immediate postoperative period.

From the Division of Gynecologic Endocrinology, Department of Obstetrics and Gynecology, Duke University School of Medicine.

Received for publication February 9, 1976.

Accepted March 3, 1976.

Reprint requests: Dr. Sezer Aksel, Department of Obstetrics and Gynecology, Duke University School of Medicine, P. O. Box 3363 Durham, North Carolina 27710.

Material and methods

Twenty-two women were evaluated. Sixteen women ranging in age from 21 to 39 years were having cyclic menses; three had been using oral contraceptives (one used Norlestrin,* 2.5 mg., and two used Ortho-Novum 1/80,† from one to three years), and three were perimenopausal (41 to 48 years old). Bilateral ovariectomy was performed for pelvic pain secondary to pelvic inflammatory disease, endometriosis, Stage I cervical cancer, or unilateral ovarian neoplasms. Each patient had at least one histologically normal ovary. Beginning on the day before operation, daily blood samples were obtained by venipuncture, at the same time of the day whenever possible. Serum was separated and stored frozen at −20° C. until assayed. All samples from a particular subject with respect to a given hormone were run in a single assay. Patients were followed closely by the attending physicans, and the occurrence of vasomotor symptoms was evaluated as objectively as possible and reported to one of the investigators. Episodes of postoperative chills and fever were taken into consideration. Exogenous estrogen was started during the study period only if the patient became

*Parke, Davis & Co., P. O. Box 118 GPO, Joseph Campau Ave. At the River, Detroit, Michigan 48232.

†Ortho Pharm. Corp., Route 202, Raritan, New Jersey 08869.

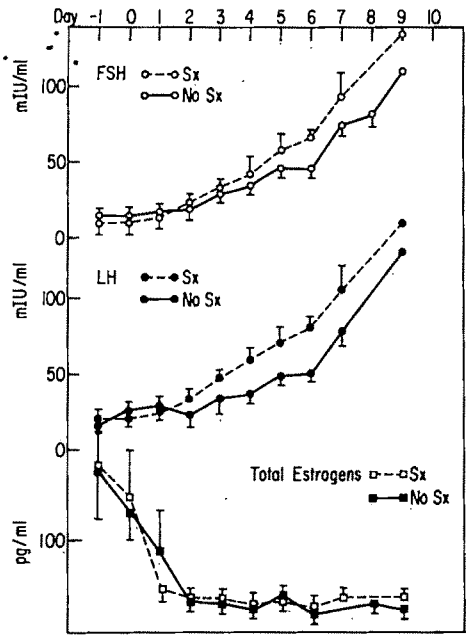


Fig. 1. Summary of findings in 16 young women undergoing castration procedures and comparison of the means of FSH, LH, and total estrogen values of the group who developed symptoms postoperatively to the group who remained asymptomatic. The vertical bars denote the standard error of the mean. Day 0 = Day of operation.

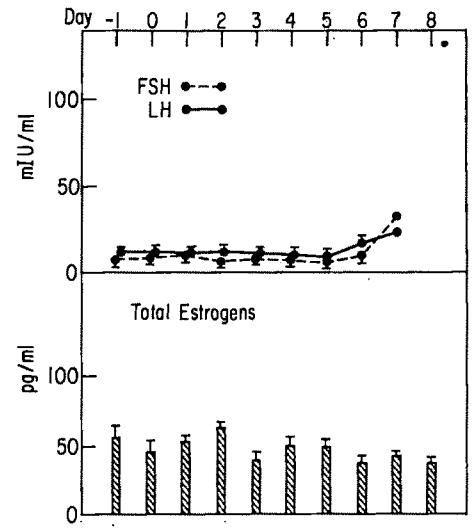


Fig. 2. Mean levels of FSH, LH, and total estrogens of three women who were using oral contraceptives prior to castration. The vertical bars denote the standard error of the mean. Day 0 = Day of operation.

acutely and severely symptomatic. Statistical comparisons were made with Student's t test.

Radioimmunoassay methods. FSH and LH levels were determined by the radioimmunoassay method of Odell and associates.[1] Gonadotropin assays were run in triplicate and were capable of measuring 4 mI.U. of the immunologic activity of FSH and LH per milliliter of serum relative to the Second International Reference Preparation for Human Menopausal Gonadotropins. The intra-assay and interassay coefficients of variation for the FSH assay were 6.1 and 6.5 per cent, and those for the LH assay were 4.9 and 5.9 per cent, respectively.

Total serum estrogens were assayed with the use of 1:35,000 dilution of sheep antiserum (Lot SF No. 1-7) to estradiol-17β-succinyl-bovine serum albumin generated in this laboratory. The 10 pg. point on the standard curve was significantly different from zero at the 95 per cent confidence limit. The cross-reactivity values of the antiserum to estrone and estriol relative to estradiol were 0.76 and 0.15, respectively. Five nanograms of testosterone, dihydrotestosterone, progesterone, 17α-hydroxyprogesterone, corticosterone, cortisol, deoxycorticosterone, 20α- and 20β-dihydroprogestone, dehydroepiandrosterone, and androstenedione displaced less radioligand than did 10 pg. of estradiol. After logit transformation, the standard curve obtained was linear from 10 to 250 pg. Assay values (mean ± S.D.) observed following the addition of 10, 25, 50, 125, and 250 pg. of estradiol to 0.5 ml. aliquots of male serum were 17.2 ± 1.9, 42 ± 3, 46 ± 5, 123 ± 5, and 236 ± 20, respectively. Intra-assay and interassay coefficients of variation were 4 to 10.5 per cent and 14.3 per cent, respectively. The assay procedure of Hotchkiss and colleagues[2] was utilized with the following modifications. Internal standard (^{3}H) estradiol-17β (about 2,000 disintegrations per minute [d.p.m.]) was added to each sample. After ether extraction, the phases were separated with the dry ice–ethanol freezing technique.[3] Following solvent evaporation, the sample was redissolved in 0.5 ml. of ethanol; 0.1 ml. was removed for recovery, and the remainder was dried. Approximately 39,000 d.p.m. (^{3}H)-estradiol-17β was incubated with antisera and unknown for one hour at room temperature. Each sample was assayed in triplicate, and the two closest determinations were averaged. The agreement of such duplicates was routinely within ±10 per cent of the mean.

Serum progestin was determined by a modification of the method described by Abraham and co-workers,[3] with the use of the antiserum (S-49 No. 6) characterized in their publication. Total serum progestins were quantitated in lieu of specific isolation of progesterone prior to assay. This was accomplished by utilization of petroleum ether for extraction, thus minimizing the potential contribution of corticoids and other hy-

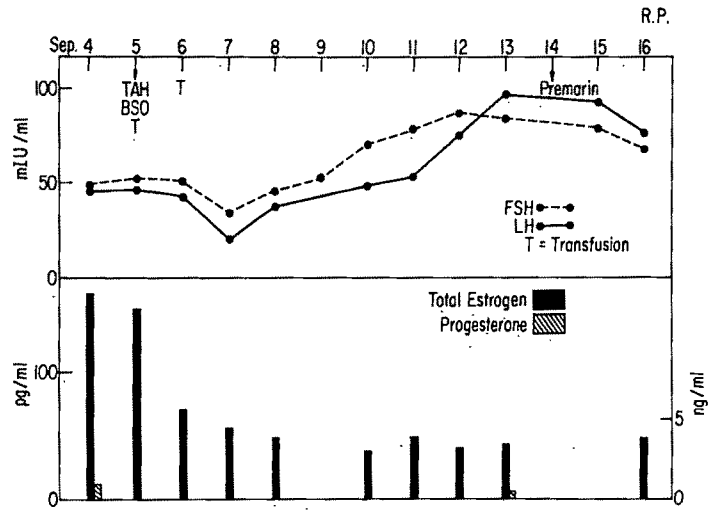


Fig. 3. Serum FSH, LH, estrogen, and progestin levels in 47-year-old perimenopausal patient with vasomotor symptoms. TAH = Total abdominal hysterectomy. BSO = Bilateral salpingo-oophorectomy.

droxylated progestins to the assay system (data not shown). (^{3}H)-progesterone was utilized in the assay system, and all values were corrected for procedural losses. The subsequent steps were virtually identical to those outlined above for the estrogen radioimmunoassay. Total serum progestin values observed in 9 normally cycling patients averaged 0.6 ± 0.3, 2.3 ± 1.7, and 8.6 ± 2.6 ng. per milliliter (±S.D.) in the follicular, midcycle, and luteal phases of the menstrual cycle, respectively.

Results

Fig. 1 summarizes the findings in 16 young cycling women who underwent surgical procedures including castration. Gonadotropin levels started to rise the third day after operation and reached castrate values within seven days. Estrogen levels fell precipitously from the time of the first postoperative day and remained at or below the 50 pg. per milliliter range starting on the second day after operation. Only six women, 37.5 per cent of the 16, developed vasomotor symptoms during their hospital stay. The estrogen values of the women who developed symptoms postoperatively were similar to those who remained asymptomatic. The LH values showed an earlier increase in the symptomatic group; however, the mean values of FSH and LH of the two groups were not statistically different from each other.

Findings for the group of three young women using a combination-type oral contraceptive prior to castration are outlined in Fig. 2. Oral contraceptive pills were discontinued the day before operation. The base-line estrogen levels of these patients were comparable to those found in castrate or postmenopausal women, and ovariectomy produced no significant change in the serum estrogen concentration. FSH and LH remained suppressed with minimal elevations noted on the seventh postoperative day. Only one of the three women complained of severe vasomotor symptoms on the third postoperative day and required estrogen treatment. This patient was using Ortho-Novum 1/80 while the other two, who remained asymptomatic, had been using Ortho-Novum 1/80 and Norlestrin, 2.5 mg., respectively, prior to operation.

Fig. 3 presents the gonadotropin, estrogen, and progestin levels of a 47-year-old perimenopausal patient with frequent "hot flushes" and abnormal bleeding due to adenomatous hyperplasia. FSH levels were elevated, and LH values were in the high normal range. Total estrogens preoperatively were in the 200 pg. per milliliter range which is compatible with preovulatory values in our laboratory. After castration, both FSH and LH continued to rise, reaching postmenopausal levels within a week. The estrogen values declined below 50 pg. per milliliter into the postmenopausal range. She complained of "hot flushes" despite the high estrogen levels prior to operation and continued to have vasomotor symptoms after bilateral oophorectomy. Estrogen therapy was instituted on the ninth postoperative day because of the severity of symptoms.

The FSH levels of another 48-year-old perimenopausal patient with dyfunctional uterine bleeding and no vasomotor symptoms were elevated to 50 mI.U. per milliliter (Fig. 4). LH and total estrogen values were normal. Following castration, both gonadotropins rose to the menopausal 'range' within

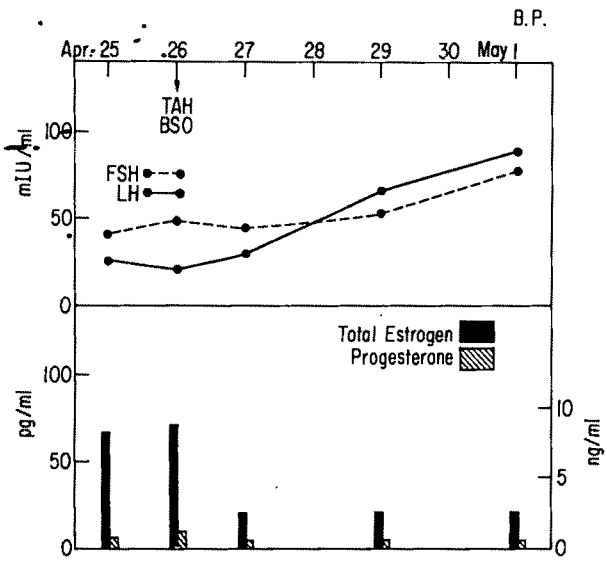


Fig. 4. Serum FSH, LH, estrogen, and progestin levels in a 48-year-old patient with abnormal uterine bleeding and no vasomotor symptoms. TAH = Total abdominal hysterectomy. BSO = Bilateral salpingo-oophorectomy.

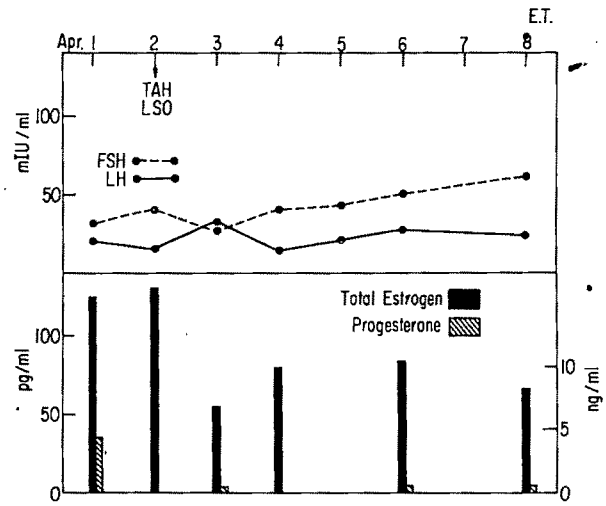


Fig. 5. Serum FSH, LH, estrogen, and progestin levels in a 41-year-old perimenopausal woman with occasional "hot flushes." Total abdominal hysterectomy and left salpingo-oophorectomy were performed, and a corpus luteum in the right ovary was resected.

one week; progestin levels remained unchanged, and estrogen values were less than 25 pg. per milliliter. This patient had no vasomotor symptoms during her hospital stay or subsequently at home. She was given topical estrogen six weeks postoperatively for atrophic vaginitis.

Fig. 5 shows the findings of a 41-year-old perimenopausal woman with infrequent "hot flushes." The FSH levels were elevated to the 40 to 50 mI.U. per milliliter range while LH values were normal. Total abdominal hysterectomy and left salpingo-oophorectomy were performed. A corpus luteum in the right ovary was resected, but this ovary was not removed since the patient requested preservation of ovarian function, if feasible. Estrogen values declined from the 120 pg. per milliliter range to the 60 to 70 pg. per milliliter level, compatible with removal of the corpus lutem, and progestin values fell concomitantly. Although the remaining right ovary of this patient maintained estrogen values characteristic of the early part of the follicular phase, FSH continued a slow, steady rise, and the patient complained of vasomotor symptoms. At the six-week postoperative visit, both FSH and LH values had reached postmenopausal levels.

Comment

The aging ovary is assumed to loose its steroidogenic potential and its capability of maintaining the hypothalamic-pituitary-ovarian homeostasis. A decrease in circulating estrogen has been commonly believed to be the cause of perimenopausal vasomotor symptoms. On the other hand, surgical menopause, which abruptly removes the major source of estrogen, is thought to be invariably associated with the onset of the "hot flush."

Castration of young cycling women resulted in a rapid decline in endogenous estrogen values (Fig. 1), but only 37.5 per cent developed vasomotor symptoms during the immediate postoperative period. The timing of the castration procedure (follicular versus luteal phase) did not seem to have a bearing on the outcome. One of the three women who used oral contraceptives prior to operation and who underwent castration (Fig. 2) complained of severe vasomotor symptoms immediately after operation. There was no statistical difference in total serum estrogen, FSH, or LH values between the group of patients with symptoms and those without symptoms.

As previously reported,[4] the first indication of failing ovarian function seems to be an elevation of FSH over the normal values. Although this may be a temporary phenomenon, it occurs prior to LH rise and appears to be a consistent finding among perimenopausal women. Two of the three perimenopausal patients presented with "hot flushes," and all three had elevated FSH, normal LH, and normal estrogen values preoperatively (Figs. 3 to 5).

The tendency to firmly believe that vasomotor symptoms are caused by a decrease or lack of endogenous estrogen has been strengthened by the clinical observation that the "hot flush" is usually relieved by the

administration of estrogen. However, this concept needs to be questioned since there is evidence that other remedies such as dithiocarbamoylhydrazine (a mild tranquilizer[5]), clonidine (an antihypertensive[6]), and medroxyprogesterone acetate (a progestin[7]) are as successful as estrogen in relieving vasomotor instability. The results of this study indicate that rising gonadotropin or declining estrogen values measured by current radioimmunoassay techniques appear to have no direct correlation to the onset of the vasomotor symptoms in the immediate postoperative period. Thus, the precise etiology of the "hot flush" remains to be elucidated.

The authors gratefully acknowledge the technical assistance of Mrs. A. Brown and Mrs. Linda Stewart.

REFERENCES

1. Odell, W. D., Rayford, P. L., and Ross, G. T.: Simplified, partially automated method for radioimmunoassay of human thyroid-stimulating, growth, luteinizing, and follicle stimulating hormones, J. Lab. Clin. Med. **70:** 973, 1967.
2. Hotchkiss, J., Atkinson, L. E., and Knobil, E.: Time course of serum estrogen and luteinizing hormone concentrations during the menstrual cycle of the rhesus monkey, Endocrinology **89:** 177, 1971.
3. Abraham, G. E., Swerdloff, R., Tulchinsky, D., et al.: Radioimmunoassay of plasma progesterone, J. Clin. Endocrinol. Metab. **32:** 619, 1971.
4. Aksel, S., and Jones, G. S.: Eiology and treatment of dysfunctional uterine bleeding, Obstet. Gynecol. **44:** 1, 1974.
5. Ferriman, D., and Purdie, A. W.: Mechanism of menopausal "hot flushes" indicated by the effect of a dithiocarbamoylhydrazine, J. Endocrinol. **31:** 173, 1965.
6. Clayden, J. R., Bell, J. W., and Pollard, P.: Menopausal flushing: double blind trial of a non-hormonal medication, Br. Med. J. **1:** 409, 1974.
7. Bullock, J. L., Massey, F. M., and Gambrell, R. D.: Use of medroxyprogesterone acetate to prevent menopausal symptoms, Obstet. Gynecol. **46:** 165, 1975.

Scanning and transmission electron microscopic studies of vaginal adenosis and the cervical transformation zone in progeny exposed in utero to diethylstilbestrol

CECILIA M. FENOGLIO, M.D.
New York, New York
ALEX FERENCZY, M.D.
Montreal, Quebec, Canada
RALPH M. RICHART, M.D.
New York, New York
DUANE TOWNSEND, M.D.
Los Angeles, California

Much attention has recently been focused on vaginal adenosis and other cervical and vaginal alterations occurring in female offspring exposed to diethylstilbestrol (DES) in utero. These alterations consist of heterotopic glandular epithelium in the vagina, a characteristic cervical transformation zone, and the frequent presence of a cervical collar, or hood. It is believed that these changes occur during embryonic differentiation of the lower genital tract following failure of squamous epithelium to migrate in a cephalad direction to replace columnar epithelium which normally lines the vagina and ectocervix. A number of cases of clear-cell carcinoma have occurred in DES-exposed girls who also had adenosis. In an attempt to characterize the cellular populations of these areas of adenosis, we have made an ultrastructural study which is herein reported.

VAGINAL ADENOSIS and other cervical and vaginal alterations which occur in female progeny exposed to diethylstilbestrol (DES) in utero are a problem which is currently receiving a great deal of attention. The lesion consists of heterotopic glandular epithelium in the vagina, a characteristic cervical transformation zone, and the frequent presence of a cervical collar, or hood. These changes are thought to occur during the embryonic differentiation of the lower genital tract as a result of the failure of the squamous epithelium to migrate in a cephalad direction to replace the columnar epithelium which normally lines the vagina and ectocervix.[1]

Histologically, the areas of adenosis appear to be composed mainly of endocervical epithelium,[2] but endometrial and Fallopian tubal[3] epithelium has also been described.

The importance of adenosis in the DES-exposed progeny was recognized after the appearance of a number of cases of clear-cell carcinoma in DES-exposed girls who had adenosis as an associated lesion. Since clear-cell carcinomas are thought to be derived from endometrial-type epithelium[4–7] and since there is controversy concerning the histologic identity of the glandular epithelium present in areas of adenosis, we believed it was important to study the lesions ultrastructurally in an attempt to characterize their cellular

From the Department of Pathology, Columbia University College of Physicians and Surgeons, and Division of Obstetrical and Gynecological Pathology, and the Cytology and Pathology Laboratories, The Sloane Hospital for Women in Columbia-Presbyterian Medical Center, New York, the Department of Pathology, McGill University, and the Division of Obstetrical and Gynecological Pathology, Jewish General Hospital, Montreal, the Department of Obstetrics and Gynecology, University of Southern California, and the Division of Gynecologic Oncology, Los Angeles County Medical Center, Los Angeles.

Presented in part to the Society of Gynecologic Oncologists, Key Biscayne, Florida, January, 1975.

Received for publication July 7, 1975.

Revised May 3, 1976.

Accepted June 29, 1976.

Reprint requests: Dr. Ralph M. Richart, 630 W. 168th. St., New York, New York 10032.

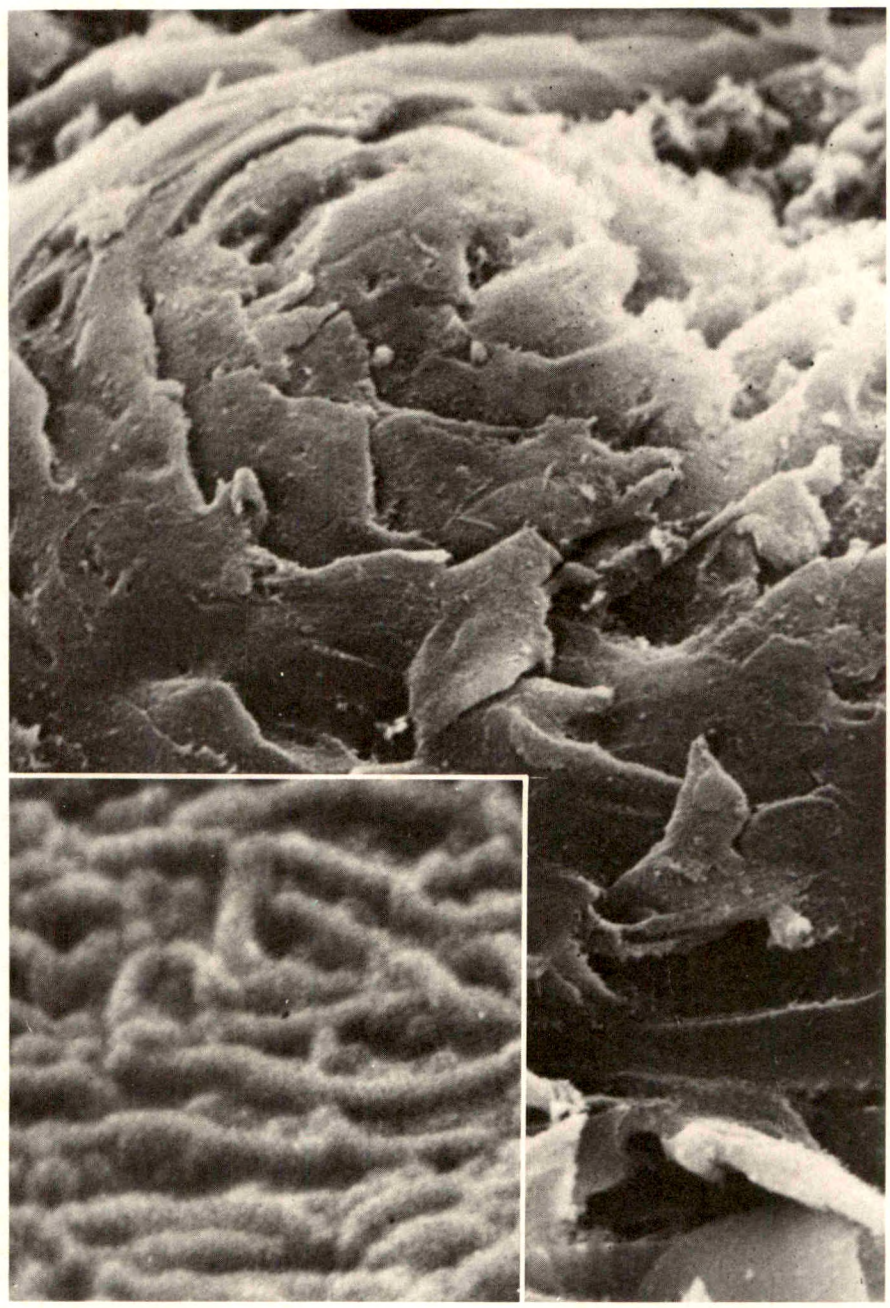


Fig. 1. Vaginal adenosis: SEM of mature transformation zone epithelium illustrating pavement-like appearance of superficial squamous cells. Cells are flat and loosely attached. (×640). Inset: High magnification of surface of superficial squamous cells which are covered with characteristic microridges. (×22,500.)

populations. This is a report of these ultrastructural studies.

Material and methods

The biopsies examined in this study were taken under colposcopic control from 32 females DES-exposed progeny. Areas of columnar epithelium or adenosis were identified on the cervix and in the vagina, and samples were removed by punch biopsy. From one to six biopsies were taken from each patient and were immediately fixed in 2.5 per cent glutaraldehyde in Sorenson's phosphate buffer for less than

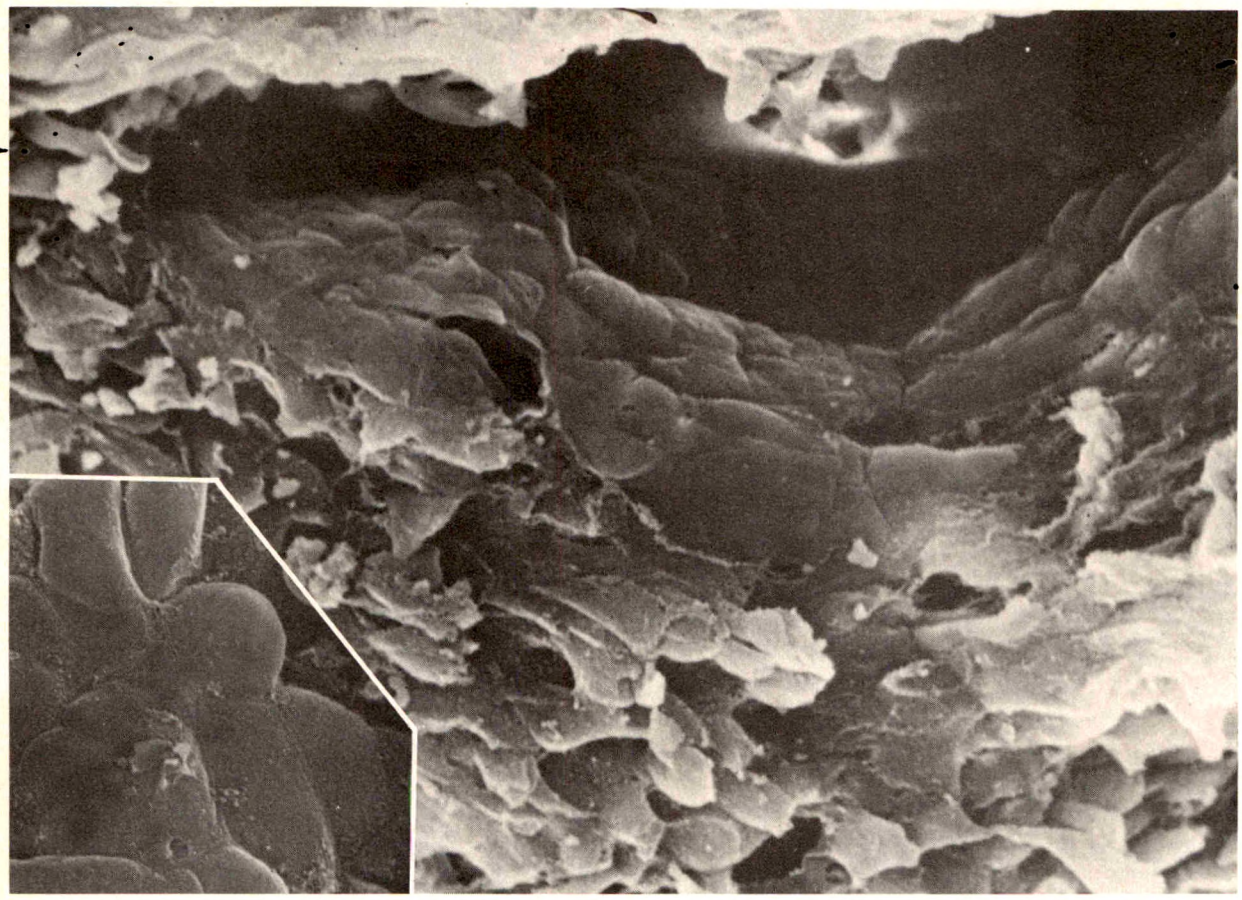


Fig. 2. Vaginal adenosis: Immature transformation zone epithelium composed of tightly packed surface cells with bulging surface membranes. Cells have irregular arrangement. (Original magnification ×4,800.) Inset. Young squamous epithelium is covered by microvillous processes, and cells are interconnected by well-developed terminal bars. (Original magnification ×10,000.)

one hour. Each specimen was then divided into two parts. Half of the specimen was processed in a routine fashion for scanning electron microscopy (SEM)[7]; the other half was processed in a routine manner for transmission electron microscopy (TEM).[7] The areas of special interest for TEM examination were chosen by examining thick sections stained with toluidine blue and trimming the Epon blocks of excess tissue. The specimens used for the SEM studies were rehydrated after SEM examination according to the method previously described[8] and were then examined histologically. Thirty-three vaginal specimens and 17 cervical specimens were examined with both SEM and TEM. Multiple blocks of each TEM specimen were examined.

Results

A prominent inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes was present in all specimens, within both the epithelium and the connective tissue. Areas of squamous metaplasia were uniformly present in the transformation zone. By SEM the surface ultrastructure of this epithelium was sometimes mature with microridges (Fig. 1), but, more commonly, it was immature and covered by short stubby microvilli (Fig. 2). The immature cells contained regular cytologic features and were arranged in the orderly pattern typically seen in an immature transformation zone.[7]

At the TEM level the squamous cells contained glycogen and were attached to one another by well-developed intercellular bridges and intercellular junctions. As the cells matured, there were increased numbers of tonofilaments. In many areas, immature squamous epithelium was found beneath the glandular epithelium and was attached to the columnar cells by well-developed cell junctions.

Typical endocervical cells were present in all specimens. Frequently short projections were found

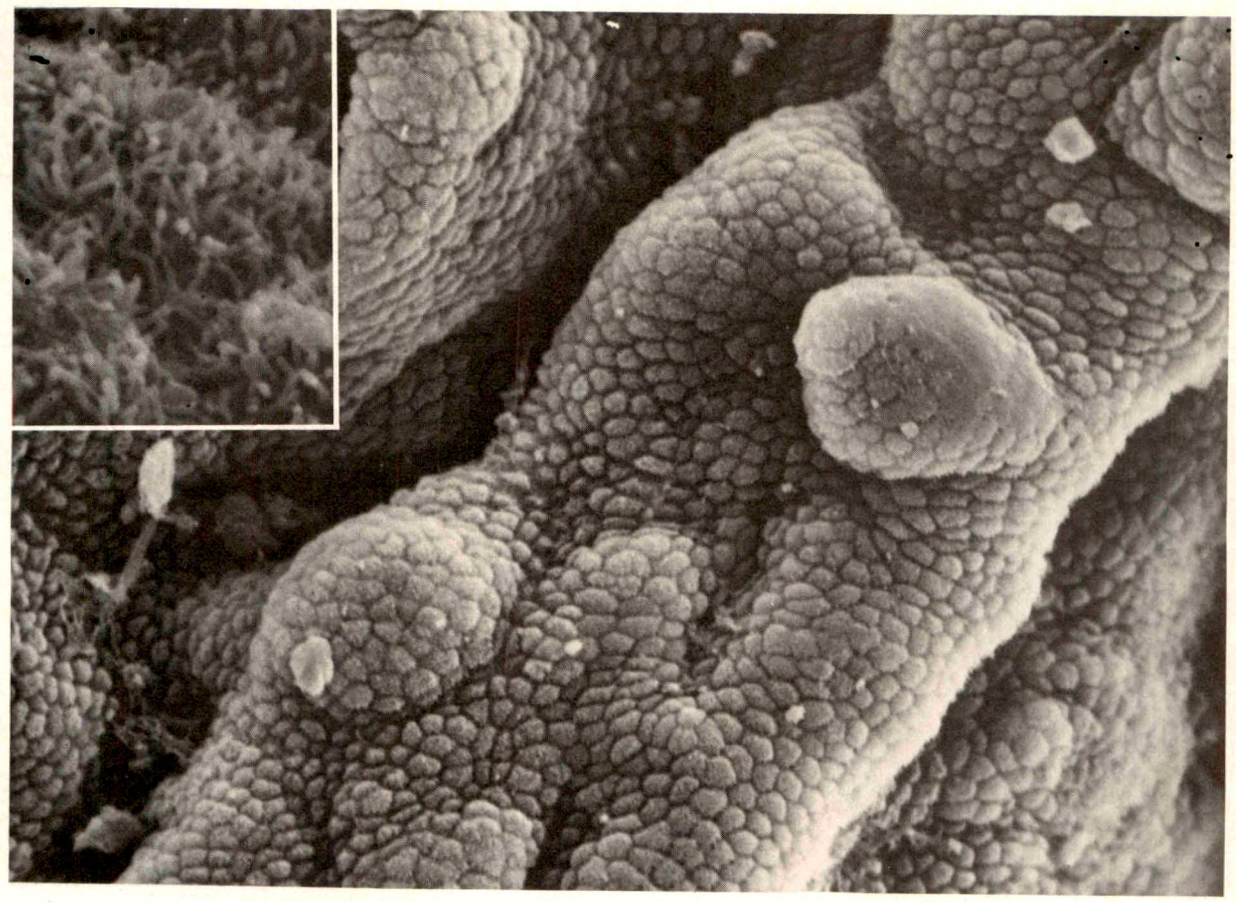


Fig. 3. Vaginal adenosis: Endocervical-type epithelium with villi. Columnar epithelial cells have a polygonal contour, and each cell is covered with abundant microvilli. (Original magnification ×4,800.) Inset. High magnification of closely packed surface microvillous projections in endocervical columnar cells. (Original magnification ×10,000.)

accounting for the grapelike appearance noted colposcopically. With SEM, these cells could be differentiated from the immature squamous cells by the presence of apical droplets of extruded mucus and long microvilli (Fig. 3 [inset]). When SEM specimens were rehydrated and examined with the light microscope, typical endocervical cells were seen.

The appearance of these cells with use of TEM was also typical for endocervical mucinous epithelium (Fig. 4). The mucinous droplets completely filled the supranuclear cytoplasm except in areas of extensive inflammation. In inflamed areas the number of secretory droplets was decreased in proportion to the severity of the inflammation. The endoplasmic reticulum was unusually prominent, and many fibrilogranular bodies (Fig. 5) and subnuclear glycogen granules (Fig. 4) were present.

In four of the cases, there were cells covered with irregular microvillous tufts among the endocervical cells (Fig. 6, *a* [inset]). The surface morphology of these cells as seen with SEM suggested normal proliferative endometrial cells.[7] TEM on similar cells clearly demonstrated that these tufts were on otherwise normal mucinous endocervical cells (Fig. 6).

In two cases, glands were seen in which the epithelium was composed of a mixture of mucin-secreting cells, non–mucin-secreting columnar cells, and ciliated cells (Fig. 7, *a*). Ultrastructurally, ciliated cells in the process of active ciliogenesis were easily identified (Figs. 7, *b* and 8). Although typical endocervical cells were also present in these areas, there were, in addition, glandular cells which contained scanty mucus, with a few uniform-sized, membrane-bound mucinous granules and associated large aggregates of glycogen and supranuclear Golgi apparatuses (Fig. 9). In view of the conspicuous amount of glycogen and the scant secretory granules, it is possible that this type of cell may be intermediate between a mature endocervical cell

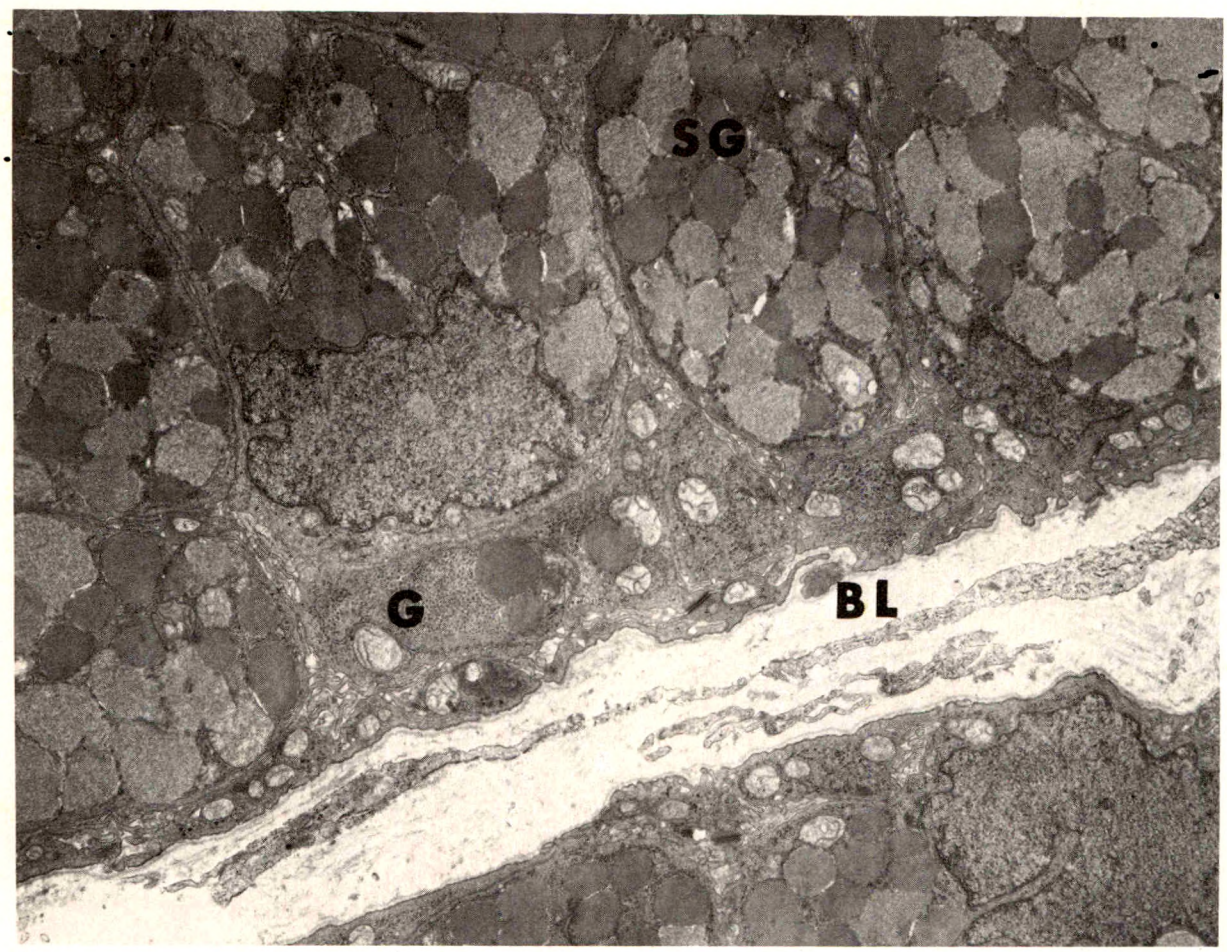


Fig. 4. Vaginal adenosis: Lining of glands consists of layers of typical endocervical-type mucinous epithelium, with basally located nuclei, abundant supranuclear mucin droplets *(SG)*, and aggregates of glycogen granules *(G)*. The stroma is separated from the epithelium by a basal lamina *(BL)*. (×3,920.)

and a mucin-devoid endometrium-type cell.

Cells were also present which were totally devoid of mucin and in which the organelles associated with pools of glycogen were concentrated in the supranuclear area. The nuclei were voluminous, and their long axes were perpendicular to the surface (Fig. 10). These types of cells were identical with those seen in endometrial glands during the early to midsecretory phase of the menstrual cycle and did not resemble nonciliated tubal epithelial cells.[7]

Comment

The derivation and nature of the columnar epithelium in the cervix and vagina of the DES progeny are not precisely known, nor is the natural history of the vaginal and cervical changes. It is also not know whether some of the DES-induced epithelial alterations should be considered premalignant or which of the several cell types identified in the cervix and vagina of these women is the progenitor of clear-cell adenocarcinoma.

The biopsies examined in this study confirm previous observations that the major part of the transformation zone is covered by endocervical epithelium and immature benign squamous epithelium of metaplastic origin. The regularity of the pattern of the metaplasia which occurs in these cases helps to differentiate it from cervical intraepithelial neoplasia (CIN)[7] in which a much greater degress of irregularity of the cell surfaces occurs. Such a differentiation is important since it has recently been suggested that there is an increased incidence of CIN in the DES progeny.[9]

In 1877, von Preushen originally described the heterotopic vaginal columnar epithelium as being en-

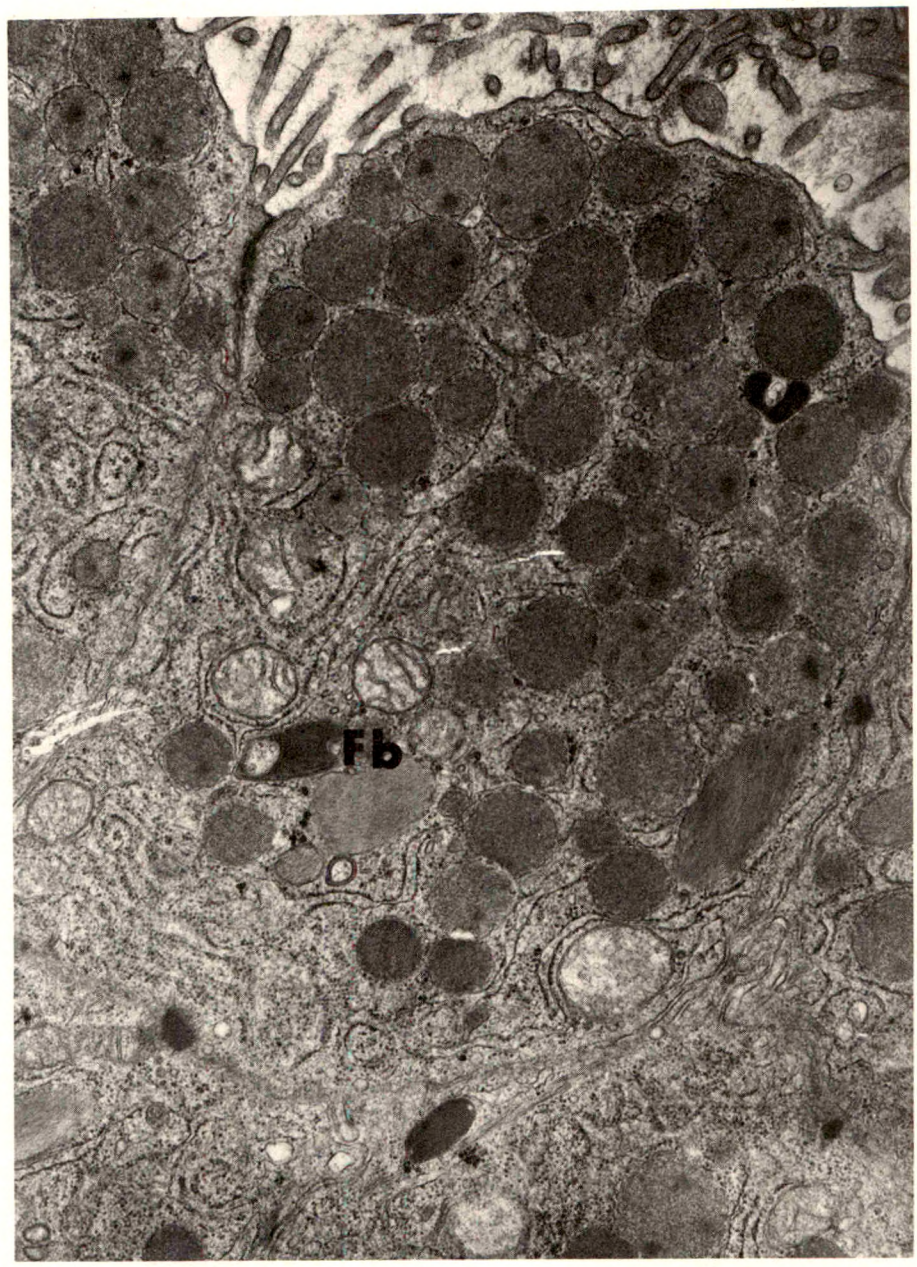


Fig. 5. Vaginal adenosis: Higher magnification of apical portion of mucinous cells with dense, membrane-bound mucin containing secretory granules associated with fibrilogranular bodies *(Fb)* and parallel membrances of glandular endoplasmic reticulum. The cell surface is lined by slender microvilli. (×17,360.)

docervical in origin.[10] More recent reports have indicated that this epithelium has the colposcopic, histologic, and cytologic features of endocervical epithelium.[2] Typical endocervical cells were present in all areas of the cervical transformation zone and in the areas of vaginal adenosis which were examined in the present study.Differences were noted between the endocervical cells of some of the DES progeny and those present in the normal endocervix. The occurrence of tufted endocervical cells in four of the 33 cases examined has not been noted previously in the human female genital tract.

On histologic grounds alone, the distinction between the various Müllerian epithelia is difficult to make and, in the presence of significant inflammation, a common finding in DES offspring, the amount of mucin pro-

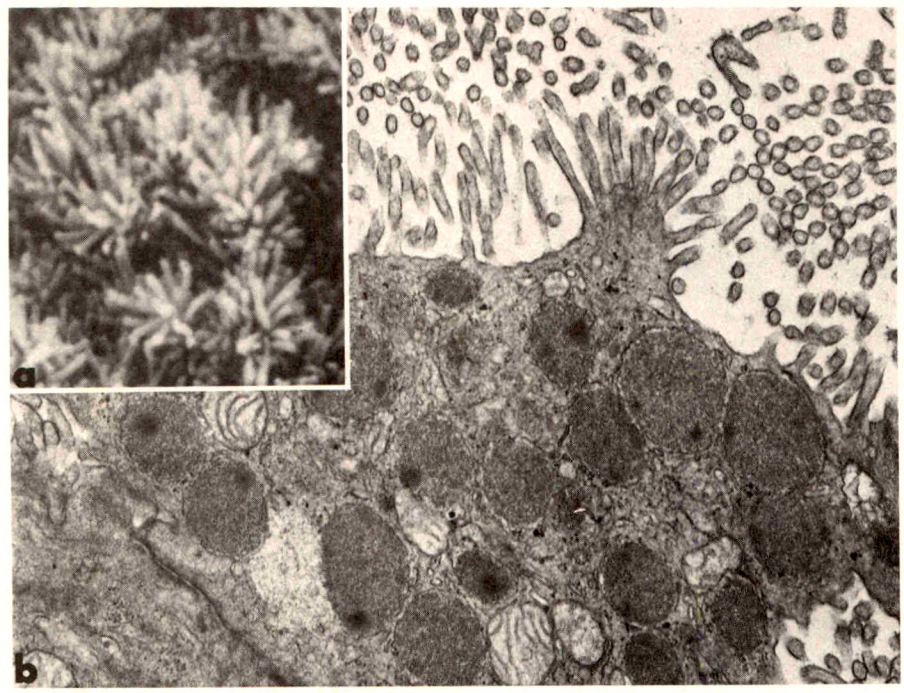


Fig. 6. *a* Vaginal adenosis: The surface of several glandular cells contains microvillous promontories. (×9,600.) *b* Promontories at the TEM level are composed of focal cytoplasmic protrusions covered by projecting microvilli. The presence of numerous mucin-containing secretory granules beneath the surface plasma membrane is typical of endocervical-type epithelium. (×14,000.)

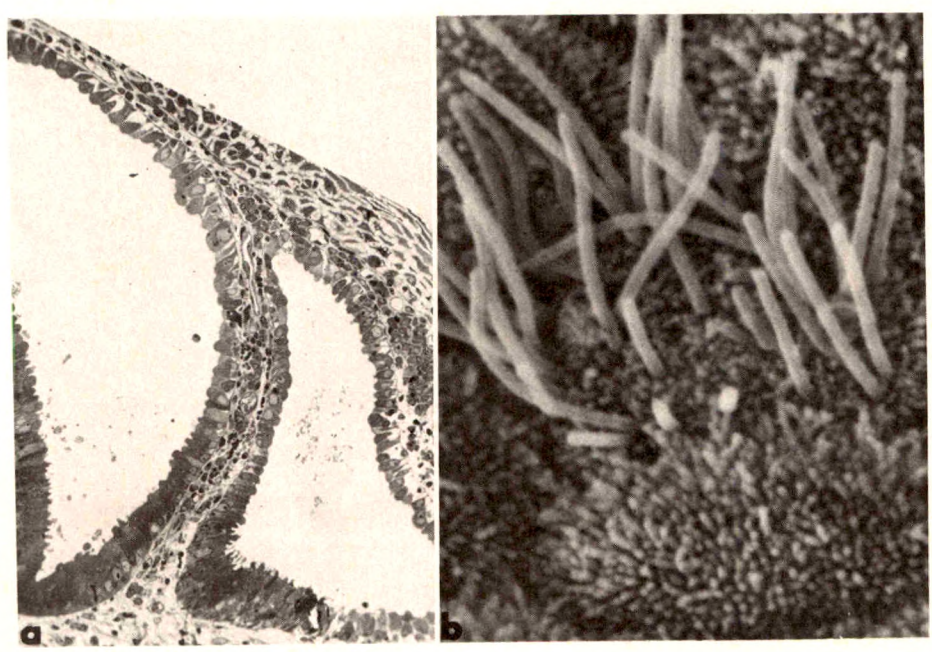


Fig. 7. *a* Vaginal adenosis: In addition to glands lined by normal endocervical epithelium, there are individual glands and clusters of glands in which epithelium is composed of an admixture of mucus-secreting cells, cells devoid of mucus droplets, and ciliated cells. Characteristically, stroma surrounding these glandular apparatuses contains numerous plasma cells. (Toluidine blue, thick section. Original magnification ×55.) *b* High-power scanning electron micrograph illustrating tufts of mature and developing ciliary shafts. Surrounding nonciliated cells are covered by abundant well-developed microvilli. (Original magnification ×8,000.)

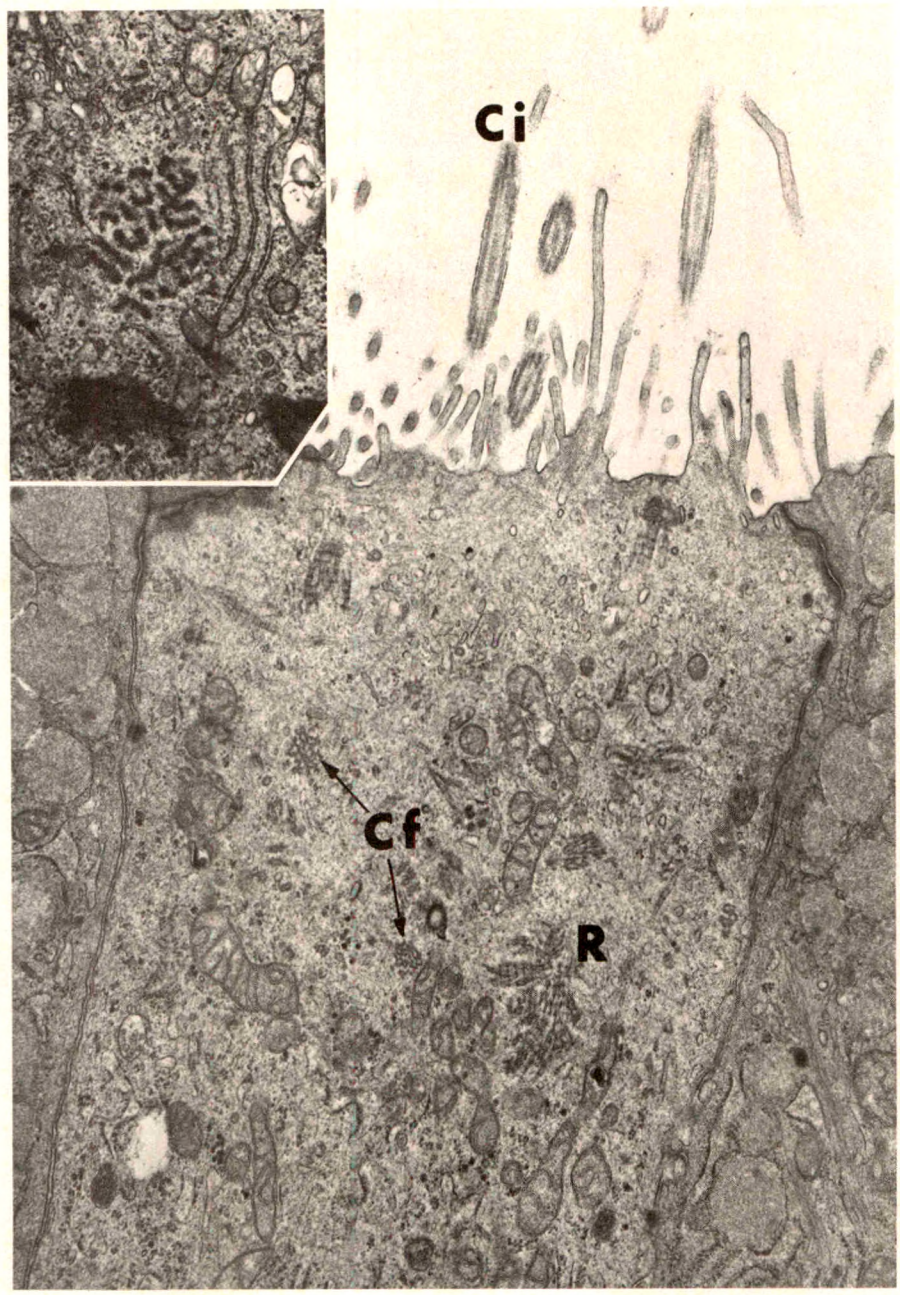


Fig. 8. Vaginal adenosis: Cell with tangentially sectioned ciliary shafts *(Ci)* and numerous cross-striated ciliary rootlets *(R)* is flanked by two mucinous endocervical cells. The ciliated cell is engaged in active ciliogenesis as evidenced by aggregates of condensation forms *(Cf)* believed to be precursors of procentrioles. (×16,940.) Inset. Detailed view of microfilamentous condensation forms. (×37,000.)

duced by endocervical cells may be markedly reduced. From an ultrastructural viewpoint it would seem that the vast majority of the columnar cells which occur in the cervix and vagina of the DES progeny are of endocervical origin. Consequently, primary neoplasia would be expected to be of the classical endocervical type. However, in the most recent report from the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females, containing 100 cases of vaginal and 70 cases of cervical clear-cell adenocarcinomas,[11] no cases of endocervical-type carcinoma were reported.

The glycogen-rich clear-cell adenocarcinomas reported to the Registry are both histologically and

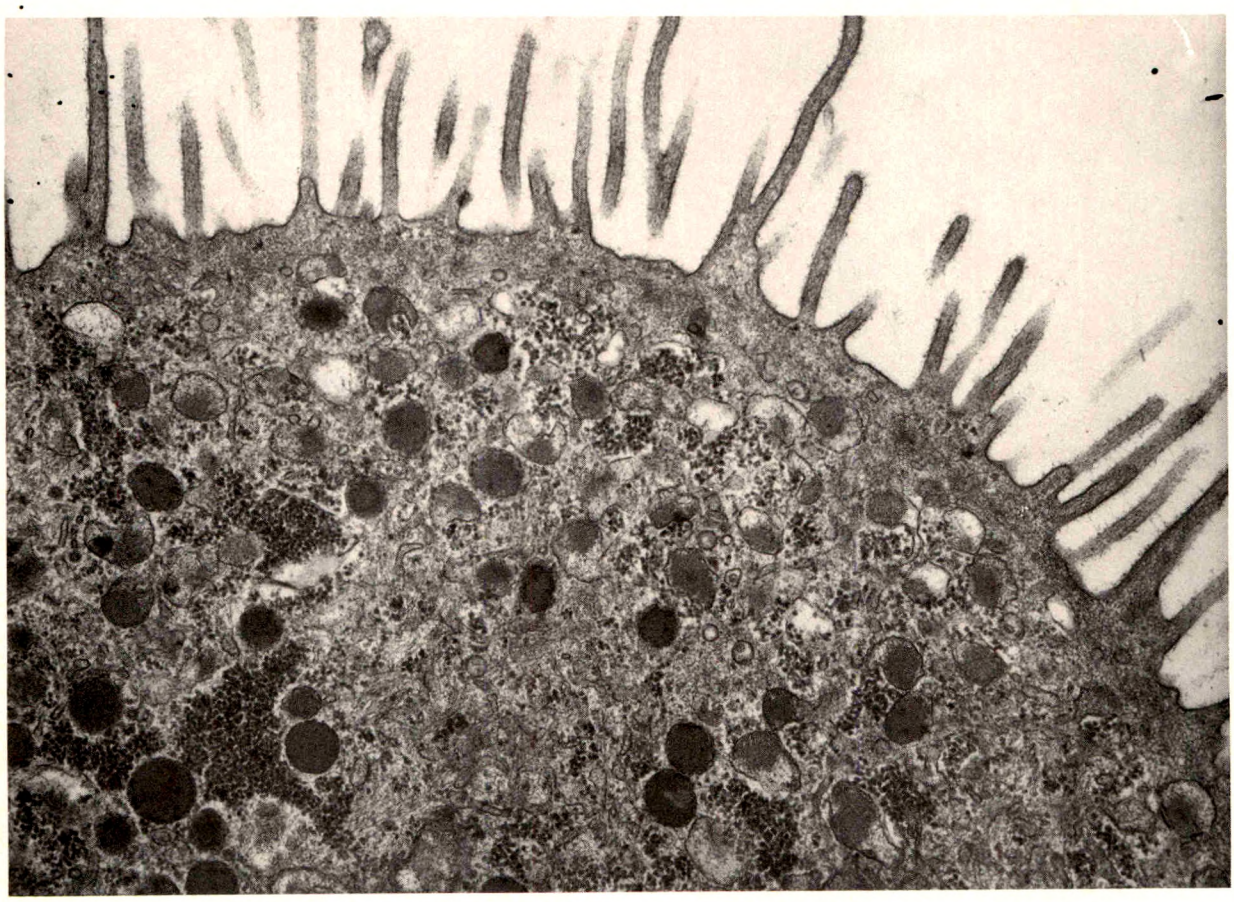


Fig. 9. Vaginal adenosis: TEM micrograph of Fig. 7, *a*, illustrating apical portion of glandular cell corresponding to cell with scanty mucus seen at light microscopic level. Cell has few mucinous secretory bodies with fine fibrilogranular content associated with large aggregates of glycogen granules, supranuclear Golgi apparatuses, and microfilaments. This type of cell may represent an intermediate form between mature endocervical and mucin-free endometrial-type cells. (Original magnification ×16,500.)

ultrastructurally[6] similar to the clear-cell cancers which arise in the uterine corpus and ovary,[7] and, in the original report of this group, an endometrioid carcinoma was also described.[12] Clear-cell cancers occurring in the female reproductive system are thought to be derived from endometrial epithelium, and in the ovary, for example, transitions between areas of endometriosis and clear-cell adenocarcinoma have been described.[4]

In the present study, we have identified a small number of cases of DES-associated changes in which the glandular epithelium was composed of an admixture of cell types including: (1) mature endocervical cells with active mucinogenesis, (2) cells intermediate between endocervical and endometrial cells with abortive mucin synthesis and abundant glycogen production, and (3) cells devoid of mucin and rich in glycogen resembling endometrial glandular cells. The fine structural organization and distribution of these cells are suggestive of a spectrum of epithelial changes consistent with a morphologic continuum, the endometrial cell type being derived from the intermediate type, which, in turn, may have its origin in either the mature endocervical cells or subcolumnar reserve cells. However, the latter cell type was not demonstrated in our material. It may also be that all three types are derived from a common Müllerian stem cell and simply occur in close proximity to one another.

The finding of endometrial-type cells in the lower genital tract of the DES progeny is consistent with the occurrence of clear-cell adenocarcinomas of the vagina in these individuals and provides a cell of origin for these cancers. The rarity of the endometrial-type cells may be an important determinant of the rarity of the



Fig. 10. Vaginal adenosis: TEM micrograph of Fig. 7, *a*, illustrating cells which on light microscopy were devoid of intracytoplasmic mucin. These cells contain no evidence of mucinogenesis, and organelles which include dilated endoplasmic reticulum, a few mitochondria, Golgi apparatuses, and free ribosomes are concentrated in a supranuclear location. The apex of an occasional cell is distended by finely granular electron-opaque material, presumably "electron-light" glycogen. The nuclei are voluminous, and their long axis is oriented perpendicular to the surface. Such cytonuclear organization closely resembles that found in epithelial cells of the endometrium. (×6,250.)

clear-cell cancers, but the number of observations made in this study is too few to draw strong conclusions regarding their incidence, and there presently is no information relative to the factor(s) which produce adenocarcinoma in the DES-exposed offspring.

REFERENCES

1. Linhartova, A.: Congenital ectopy of the uterine cervix, Int. J. Gynecol. Obstet. **8:** 653, 1970.

2. Stafl, A., Mattingly, R. F., Foley, D. V., and Fetherston, W. C.: Clinical diagnosis of vaginal adenosis, Obstet. Gynecol. **43:** 118, 1974.

3. Hart, W. R., Townsend, D. E., Aldrich, J. O., Henderson, B., and Roy, M.: Histopathologic features of vaginal adenosis and related changes in diethylstilbestrol-exposed females, Lab. Invest. **32:** 10, 1975. (Abst.)
4. Scully, R. E., and Barlow, J. F.: "Mesonephroma" of ovary: Tumor of Müllerian nature related to endometrial carcinoma, Cancer **20:** 1405, 1967.
5. Silverberg, S. G., and De Giorgi, L. S.: Clear cell carcinoma of the endometrium, Cancer **31:** 1127, 1973.
6. Silverberg, S. G.: Ultrastructure and histogenesis of clear cell carcinoma of the ovary, Am. J. Obstet. Gynecol. **115:** 394, 1973.
7. Ferenczy, A., and Richart, R. M.: Female Reproduction System: Dynamics of Scanning and Transmission Electron Microscopy, New York, 1974, John Wiley & Sons, Inc.
8. Fenoglio, C. M., Ferenczy, A., and Richart, R. M.: Mucinous tumors of the ovary. I. Ultrastructural studies of mucinous cystadenomas with histogenetic considerations, Cancer **36:** 1709, 1975.
9. Stafl, A., and Mattingly, R. F.: Vaginal adenosis—A precancerous lesion? Am. J. Obstet. Gynecol. **120:** 666, 1974.
10. Sandberg, E. C.: The incidence and distribution of occult vaginal adenosis, Am. J. Obstet. Gynecol. **101:** 322, 1968.
11. Herbst, A. L., Robboy, S. J., Scully, R. E., and Poskanzer, D. C.: Clear cell adenocarcinoma of the vagina and cervix in young girls: Analysis of 170 Registry Cases, Am. J. Obstet. Gynecol. **119:** 713, 1974.
12. Herbst, A. L., and Scully, R. E.: Adenocarcinoma of the vagina in adolescence: A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas), Cancer **25:** 745, 1970.

Hysterosalpingographic follow-up of laparoscopic sterilization

HAMID H. SHEIKH, M.D.

Louisville, Kentucky

Two hundred and fifty of 323 laparoscopically sterilized patients had hysterosalpingographic (HSG) follow-up. A Foley catheter was used in hysterosalpingography. Of these patients, 3.6 per cent demonstrated fistula; 1.2 per cent were found to have round ligament burns, and 0.618 per cent became pregnant. Mechanism of fistula formation, prevention, and management is discussed. The incidence of intrauterine pregnancy and ectopic pregnancy after laparoscopic sterilization is discussed, and the literature is reviewed. Based on these data, it is concluded that HSG follow-up is helpful in teaching institutions and where the laparoscopic sterilization is carried out by inexperienced operators. Routine HSG follow-up is not recommended.

LAPAROSCOPIC FULGURATION has become a commonly performed sterilization procedure. As its popularity has increased, its use has moved from the medical centers to the small community hospitals and from an inpatient to an outpatient procedure. The realiability of this procedure is yet to be documented. The long-term pregnancy rate is not yet available.

The mechanism of sterilization by fulguration is clear. Fulguration results in heat burn, inflammation, fibrosis, scarring, and obstruction of the tubes.[1] In its earlier stages of development, the effectiveness of tubal sterilization was tested by injection of methylene blue through the cervix and uterus immediately after the procedure. This poststerilization procedure was abandoned as it resulted in fistulas by opening the raw, burned ends of the tubes.[2]

Hysterosalpingographic (HSG) follow-up has been used with varying degrees of enthusiasm since the introduction of laparoscopic sterilization procedures.[1–3, 5–7] After 500 laparoscopic procedures, Steptoe[3] performed 250 HSG follow-ups three months after the operation and described it as a mixed blessing. Iatrogenic fistula was considered the greatest drawback. However, he continued the HSG follow-up after the sterilization when it was preceded by voluntary interruption of pregnancy.

Thompson and Wheeless[1] did not use HSG follow-up as a routine. In three of their patients who were thought to be pregnant before sterilization, HSG showed well-occluded tubes.

Jordan and associates[2] reported 910 laparoscopic sterilizations, of which 443 patients had HSG follow-up. In 60 who had HSG follow-up six weeks postoperatively, 22 had spillage. Of the 383 who had HSG follow-up 12 weeks postoperatively, only eight had spillage. These authors concluded that cutting of the tube during the coagulation procedure is not necessary and HSG follow-up is not indicated when the procedure is done by experienced operators. HSG follow-up, if done, should be undertaken after 12 weeks, and, if spillage is found, the patient should be followed according to the findings.

Peterson and Behrman[5] followed 50 cases of a series of 200 laparoscopic sterilizations with hysterosalpingography. They concluded that hysterosalpingography was not useful and that it might cause iatrogenic fistula formation. Yuzpe and associates[4] agreed with Peterson and Behrman and did not use HSG follow-up on their 50 patients with laparoscopic sterilization. Liston and associates[6] performed HSG follow-up on 78 patients in a series of 260 laparoscopic sterilizations but made no comments on such follow-up.

Black[7] followed 66 patients with hysterosalpingography in a series of 300 laparoscopic procedures and commented that properly performed hysterosalpingography at three-month intervals does not cause iat-

From the Department of Obstetrics and Gynecology, University of Louisville School of Medicine.

Received for publication November 3, 1975.

Revised March 2, 1976.

Accepted March 9, 1976.

Reprint requests: Dr. Hamid H. Sheikh, Hunter Foundation, 212 N. Upper St., Lexington, Kentucky 40507.

Table I. Comparison of results

Series	*No. of laparoscopic tubal fulgurations*	*No. with HSG follow-up*	*No. with fistula*	*No. with round ligament burns*	*Pregnancies*
Jordan and associates[2]	910	443*	30	?	?
Liston and colleagues[6]	760	78	3	2	4
Steptoe[3]	500	250	?	?	1†
This series	323	250	9‡	2	2
Black[7]	300	66	3	?	?
Peterson and Behrman[5]	200	50	?	?	1

*HSG follow-up was done in 60 patients after six weeks. Twenty-two had fistula formation.

†Ectopic pregnancy.

‡In three, the fistula closed spontaneously.

rogenic fistula. Black believes hysterosalpingography has contributed to the improvement of the technique of laparoscopic sterilization.

The aim of this study is to determine the failure of laparoscopic sterilization in regard to fistula formation, round ligament fulguration, and pregnancy rate and to estimate if any improvement can be made in the laparoscopic sterilization technique by reviewing the HSG findings.

Material and methods

From July, 1972, to March, 1975, 323 laparoscopic sterilizations were performed in the Louisville General Hospital, and HSG follow-up was carried out in 250 patients. All HSG procedures were carried out by the same operator three months or more postoperatively. The laparoscopic technique was basically the same, but the operators varied in experience.

Hysterosalpingograms, with the use of the Foley catheter tecnhique and a water-soluble radiopaque material,* were obtained in all patients.[8, 9] With the use of fluoroscopic control, x-ray films (usually two) were made. The pressure was minimal at first and increased with the second x-ray. The number of films and timing varied according to the fluoroscopic findings.

The interpretations are as follows:

1. If the dye extravasates and outlines the tube, the tube is either intact and the round ligament is burned, or the tube has recanalized.

2. If there is partial visualization of the tube, the tube is blocked at the site.

3. If the dye is extravasated in a small amount and seems pocketed, there is spillage in an area of adhesions at the site of fulguration.

4. Typical venous and lymphatic outlining can be interpreted easily as spillage in the venous and lymphatic plexus.

5. Gross spillage, resembling venous extravasation as well as free spillage in the peritoneal cavity, will be discussed later on.

6. Lack of outlining of the tube but the presence of dye freely in the pelvis in the form of crescentic shadows settling in the dependent part of the pelvis is interpreted as a tuboperitoneal fistula.

To clarify the result in No. 3, repeat hysterosalpingography is done in four to six weeks, and the patient is then managed according to the results. If the pocketed spillage persists, the patient is resterilized.

If no more spillage occurs, it is believed that there is complete occlusion of the tubes.

Situation No. 5 requires further clarification. In this case, the Foley catheter is left in the uterus, and an upright film is taken. If the dye has disappeared, the interpretation is venous spillage. If the dye is present and gravitates to the "dependent" part of the pelvis, it confirms the spillage in the peritoneal cavity and in the venous plexus.

The technique of repeat operation is as follows. Laparotomy or laparoresterilization techniques are used. In both cases the Foley catheter is inserted into the uterus or the vacuum cannula is applied to the cervix, and methylene blue is injected during the procedure. The site of the fistula is noted, and resterilization is carried out. Recoagulation by laparoscopy was done in three patients. Following resterilization, the patient is followed by the routine method.

*Salpix, Ortho Pharm. Corp., Route 202, Raritan, New Jersey 08869. Sinografin, E. R. Squib, P. O. Box 4000, Princeton, New Jersey 08450.

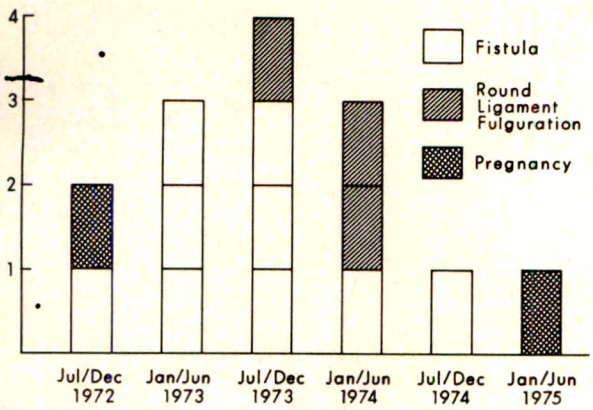


Fig. 1. Incidence of fistulas, round ligament fulguration, and pregnancy.

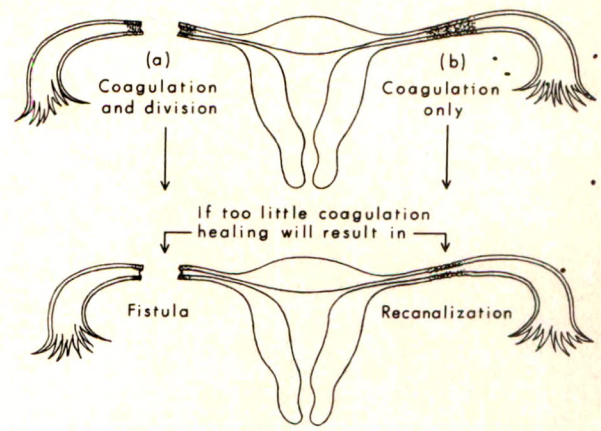


Fig. 2. Mechanism of fistula or patency.

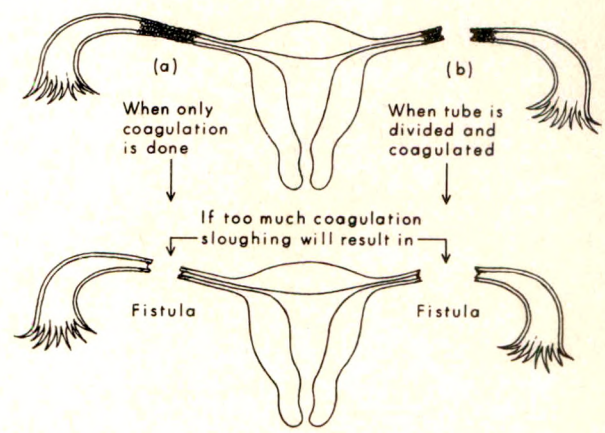


Fig. 3. Mechanism of fistula.

Results

Twelve patients of the 250 who had HSG graphic follow-up had spillage of radiopaque material in the peritoneal cavity. Of these 12, five had repeat hysterosalpingography: Two were confirmed to have spillage, and three did not show further spillage which was interpreted as showing occluded tubes. Six patients had re-exploration: Three had laparoscopy; two had laparotomy, and one had a vaginal hysterectomy. Three of these had the round ligament burned instead of the Fallopian tubes. During this study period, two patients became pregnant. One of these failed to return for the HSG follow-up. The other patient showed a fistula after hysterosalpingography and was resterilized by fulguration. Repeat hysterosalpingography confirmed that the tubes were occluded, but she later became pregnant.

The over-all results are as follows. Of the laparoscopically sterilized patients, 77.38 per cent were followed with hysterosalpingography; 3.6 per cent of these had a fistula, of which 1.2 per cent were found to have spontaneous occlusion of the fistula on repeat hysterosalpingography and 1.2 per cent had round ligament burns. The short-term follow-up pregnancy rate was 0.618 per cent. The results are compared with those of other authors in Table I.

During the last three years, we have found a decrease in the incidence of fistula (uteroperitoneal) and round ligament coagulation. This may reflect the benefit of HSG follow-up (Fig. 1).

Comment

Complete coagulation of a segment of the tube results in fibrosis and occlusion of the lumen.[1] If the tube is also divided at the coagulation site, it may or may not increase the efficiency of the sterilization. Rather, if a fistula does develop, division of the tube is a predisposing factor to pregnancy, especially ectopic pregnancy.[3] The mechanism of fistula formation is not clear as to whether inadequate coagulation or overcoagulation is the causative factor. In the first instance, healing may occur. If division of the tube is also done, a fistula may result.

If only coagulation is done, the tubes may return to their normal condition, resulting in an increased chance for either intrauterine or ectopic pregnancy due to distortion of the tubal lumen (Fig. 2).

In the second instance, overcoagulation may result in necrosis and sloughing of the tubal portion, predisposing to a fistula formation which, in turn, increases the chances for intrauterine or ectopic pregnancy (Fig. 3). The occurrence of ectopic pregnancy after laparoscopic tubal fulguration has been well documented.[1, 3]

In teaching institutions, operators in training might mistakenly coagulate the round ligament instead of the

tubes. Introduction of the teaching laparoscope has reduced this possibility.

Excessive pressure during hysterosalpingography has been blamed for iatrogenic fistula formation; therefore, the pressure used during hysterosalpingography should be kept at a minimum to avoid iatrogenic fistula. In our experience, the use of the Foley catheter for hysterosalpingography has reduced the possibility of fistula formation due to the HSG procedure. In the multiparous patient, the Foley catheter will slip out of the cervix or the Foley bulb will burst if too much pressure is applied.

There is an objection that the tip of the end of the Foley catheter might block the ostium of the tube. This was avoided by rotating the catheter. If a uteroperitoneal fistula is present, there is an increased incidence of ectopic or intrauterine pregnancy after hysterosalpingography because of the therapeutic value of lubrication of the tubal lumen and breakage of adhesions,[3, 11, 12] but HSG is not responsible for this. If a fistula is found, the patient is instructed regarding additional contraception, and the fistula is evaluated further.

If hysterosalpingography is carried out during or immediately after menstruation, pelvic veins may be visualized which occasionally may be a source of confusion. To remove such confusion, hysterosalpingography should be done in the proliferative period of the menstrual cycle. Differentiation from peritoneal spillage can be accomplished by delayed and upright x-ray films.

It has been our custom, after ruling out the possibility of round ligament burn, to perform an exploratory laparotomy and religate the tubes. For round ligament burns, repeat laparoscopic fulguration is quite practical. However, according to our experience, the fistula usually persists after repeat coagulation. This occurred in one patient who still has a fistula after the third coagulation.

The reasoning for this is that the first coagulation is usually near the cornual end and the fistula is usually between the uterus and the peritoneal cavity. Repeat coagulation does not close this type of fistula. If we know that the first coagulation is in the ampullary portion or near the fimbrial end, repeat laparoscopic coagulation is possible.

I have had a case in which a fistula was noted on the left side after hysterosalpingography. At the time of exploration, only the left tube was ligated. Unfortunately this patient later became pregnant. Therefore, even if the fistula is unilateral on repeat operation, bilateral sterilization should be done.

With all the possible complications of hysterosalpingography, are we justified in following up all laparoscopic sterilizations with hysterosalpingography?[10] It is certainly not recommended that HSG follow-up be performed routinely after procedures done by experienced operators unless there is an indication. However, it should be carried out in teaching institutions and in places where this procedure is in its initial stages.

The only complications of hysterosalpingography during this study were uterine cramps and vasomotor symptoms. The use of a Foley catheter has helped to decrease the incidence of complications and discomfort to the patient during hysterosalpingography. Occlusion of the tubal lumen by spasm during hysterosalpingography is possible even after tubal fulguration and can be a source of confusion if a tube is patent. In a doubtful situation, repeat HSG with sedation can help. For a definite evaluation of the incidence of pregnancy after laparoscopic sterilization, long-term follow-up is required. HSG follow-up is recommended in selected cases, preferably to be carried out with the Foley catheter technique.

I am grateful to Drs. Douglas Haynes and Marvin A. Yussman for critical review of the manuscript and to Dr. John T. Queenan, Chairman of the Department of Obstetrics and Gynecology, for encouragement and valuable suggestions given during the study period. I am also indebted to the x-ray department personnel for their help in carrying out this study.

REFERENCES

1. Thompson, B., and Wheeless, R. C.: Outpatient sterilization by laparoscopy. A report of 666 patients, Obstet. Gynecol. **38:** 912, 1971.
2. Jordan, J. A., Edwards, L., Pearson, J., and Maskery, P. J.: Laparoscopic sterilization and follow-up hysterosalpingogram, J. Obstet. Gynecol. Br. Commonw. **78:** 460, 1971.
3. Steptoe, P. C.: Recent advances in surgical methods of control of fertility and infertility, Br. Med. Bull. **26:** 60, 1970.
4. Yuzpe, A. A., Allen, H. H., and Collins, J. A.: Tubal sterilization. Methodology, postoperative management and follow-up of 2,933 cases, Can. Med. Assoc. J. **107:** 115, 1972.
5. Peterson, E. P., and Behrman, S. J.: Laparoscopic tubal sterilization, Am. J. Obstet. Gynecol. **110:** 24, 1971.
6. Liston, W. A., Bradford, W. P., Downie, J., and Kerr, M. G.: Laparoscopy is a general gynecologic unit, Am. J. Obstet. Gynecol. **113:** 672, 1972.
7. Black. W. P.: Sterilization by laparoscopic tubal elec-

trocoagulation: An assessment, AM. J. OBSTET. GYNECOL. **111:** 979, 1971.
8. Ansari, A. H., and Arronet, G. H.: Pneumohysterosalpingography in infertility and related gynecologic conditions. The Foley catheter technique, Fertil. Steril. **17:** 442, 1966.
9. Parekh, M. C., and Arronet, G. H.: Diagnostic procedures and methods in the assessment of female pelvic organs with special reference to infertility, Clin. Obstet. Gynecol. **15:** 1, 1972.
10. Siegler, A. M.: Dangers of hysterosalpingography, Obstet. Gynecol. Survey **22:** 284, 1967.
11. Wahby, O., Sobrero, A. J., and Epstein, J. A.: Hysterosalpingography in relation to pregnancy and its outcome in infertile women, Fertil. Steril. **17:** 520, 1966.
12. Mackey, R. A., Glass, R. H., Olson, L., and Vaidaya, R.: Pregnancy following hysterosalpingography with oil and water soluble dye, Fertil. Steril. **22:** 504, 1971.

The significance of measurement of human placental lactogen, human chorionic gonadotropin, and carcinoembryonic antigen in patients with ovarian carcinoma

NAGUIB A. SAMAAN, M.D., PH.D.
JULIAN P. SMITH, M.D.
FELIX N. RUTLEDGE, M.D.
PAMELA N. SCHULTZ, B.S.
Houston, Texas

Human placental lactogen (HPL or HCS), the beta subunit of human chorionic gonadotropin (β-HCG), and carcinoembryonic antigen (CEA) were measured by a specific radioimmunoassay in plasma of 65 patients with ovarian cancer. Fifty-one patients had epithelial tumors, while 14 had germ cell tumors. It was found that 47 patients (72 per cent) had high levels of plasma HPL, 29 patients (45 per cent) had high levels of plasma β-HCG, and 34 patients (52 per cent) had high levels of plasma CEA, but there was no correlation between these protein marker levels in different patients. Twenty of these patients were studied before and after operation and during chemotherapy and/or radiotherapy. There was no consistent correlation between these marker levels and the course of the disease. These data suggest that measurement of HPL, β-HCG, and CEA in sera of patients with ovarian cancer is not of value in assessing the clinical status of the patients or in determining the effect of therapy.

THE ECTOPIC production of polypeptide hormones by neoplams may be useful in early diagnosis of malignant disease.[1–4] Recently, attention has been focused on carcinoembryonic antigen (CEA) and ectopic placental hormones, such as placental lactogen (HPL or HCS) and the beta subunit of chorionic gonadotropin (β-HCG),[5–7] as specific markers of neoplasms.

The problems in early diagnosis and follow-up of ovarian cancer differ from those of cancers of the cervix, endometrium, vagina, and vulva. The ovary, as compared to the cervix and endometrium, is inaccessible to smears or inspection except by complicated and invasive clinical techniques.

This paper evaluates the significance of the measurement of HPL, β-HCG, and CEA as a marker in the plasma of 65 patients with ovarian cancer. Twenty of these patients were studied before and during therapy.

Material and methods

Fifty-one patients with epithelial cancer and 14 patients with malignant germ cell tumors were studied. The 51 patients with the ovarian epithelial cancers included 36 with serous tumors, 10 with poorly differentiated adenocarcinomas, three with endometrioid cancer, and two with mucinous cancer. The 14 patients with malignant germ cell tumors included three with malignant teratomas, two with dysgerminomas, eight with embryonal carcinomas, and one with choriocarcinoma (Table I).

The plasma levels of the immunoreactive HPL, β-HCG, and CEA were measured by previously described methods.[8–10] The basal plasma levels of these

From the Section of Endocrinology, Department of Medicine and Department of Gynecology, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute.

Supported by American Cancer Society Grant No. PDT 41D and the Grant CA-05831-15 from the National Institutes of Health, United States Public Health Service.

Received for publication October 6, 1975.

Accepted February 3, 1976.

Reprint requests: Dr. Naguib A. Samaan, Chief, Section of Endocrinology, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Ave., Houston, Texas 77030.

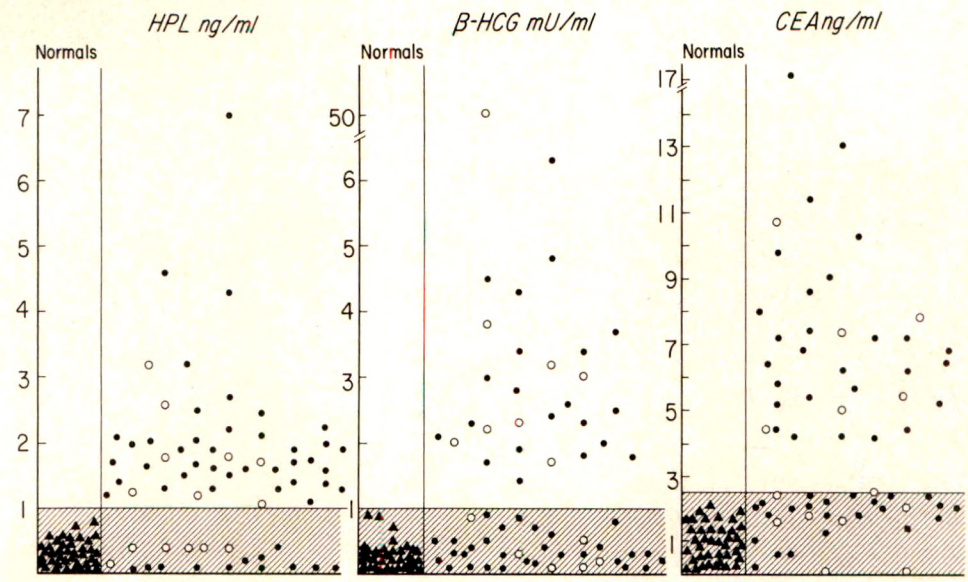


Fig. 1. Levels of HPL, β-HCG, and CEA in 65 patients with ovarian cancer compared to those found in 40 normal subjects (▲). Fifty-one patients had epithelial tumors (●) and 14 had malignant germ cell tumors (○). Forty-seven patients (72 per cent) had high plasma HPL, 29 patients (45 per cent) had high plasma β-HCG, and 34 patients (52 per cent) had high plasma CEA.

proteins were measured in 65 patients. Twenty patients were studied before and during therapy. The results obtained during therapy were correlated with the clinical picture of the disease and are summarized in Table II. The sensitivity of the HPL assay was as low as 0.5 ng. per milliliter; it was 0.5 mU. per milliliter for β-HCG and 1.25 ng. per milliliter for CEA. In each assay for these markers, plasma samples from 15 normal nonpregnant subjects of 20 to 60 years of age were included in each assay run to serve as a control. All plasma samples from each patient were measured in duplicate the same day to avoid interassay variation. In our laboratory, the intra-assay variation does not exceed 3 per cent. The plasma level of these markers was considered to be high if the value obtained was above the normal range in at least two assays done on different days.

Results

Thirty-nine of the 51 patients with epithelial tumors (76 per cent) and eight of the 14 patients with malignant germ cell tumor (57 per cent) had abnormally high plasma HPL levels. Twenty-one patients (41 per cent) with epithelial tumors and eight patients (57 per cent) with the germ cell variety had high plasma β-HCG. Twenty-eight patients (55 per cent) with ovarian epithelial tumors and six patients (43 per cent) with germ cell tumors had abnormally high plasma CEA (Fig. 1). If all the patients are considered together, 72

Table I. The incidence of abnormally high ectopic HPL, β-HCG, and CEA in 65 patients with ovarian cancer

Pathologic type	*No. of patients*
Epithelial	
Serous	36
Poorly differentiated adenoma	10
Endometrioid	3
Mucinous	2
Total	51
High plasma HPL	39 (76%)
High plasma β-HCG	21 (41%)
High plasma CEA	28 (55%)
Germ cell	
Mixed	3
Dysgerminoma	2
Embryonal	8
Choriocarcinoma	1
Total	14
High plasma HPL	8 (57%)
High plasma β-HCG	8 (57%)
High plasma CEA	6 (43%)

Table II. The incidence of clinical correlation with ectopic HPL, β-HCG, and CEA in 20 patients with the epithelial type of ovarian cancer

Correlation	*HPL*	*β-HCG*	*CEA*	*All markers*	*One or more markers*
Good	6	3	3	0	11
None	14	17	17	20	9

per cent had abnormally elevated plasma HPL, 45 per cent had high β-HCG, and 52 per cent had high CEA (Table I).

Twenty of these patients with epithelial tumors were studied before and after operation and during chemotherapy and/or radiotherapy for at least two years. Each plasma marker level was compared with the clinical picture. If there was no clinical evidence of the disease and the marker level was not elevated, this was considered a good correlation. If there was clinically detectable disease, primary or metastatic, and the marker level was elevated, this was also considered a good correlation. In some instances, a marker value was elevated and there was no clinical evidence of disease; however, at a later date, the disease became clinically evident, and this was also considered a good correlation. Conversely, if there was detectable disease but the marker level was not elevated, this was considered to be no correlation. If there was clinically detectable disease which was responding to therapy and the marker value was either not elevated or elevated but not decreasing, this was considered to be no correlation.

From the analysis of the clinical picture and plasma HPL, β-HCG, and CEA levels, this study showed that six patients showed good correlation between the plasma HPL level and the clinical course of disease; three patients showed good correlation between the plasma β-HCG level and the clinical course; three patients showed good correlation between the plasma CEA level and the clinical course of disease.

No patient showed good correlation between the clinical course of the disease and all three marker levels. However, 11 patients showed good correlation between the clinical course of the disease and at least one or more of the three marker levels. The remaining nine patients showed no correlation between the clinical course of the disease and any of the three marker levels (Table II).

Comment

Sixty-five patients with ovarian cancer were available for analysis of correlation of disease with the concentrations of plasma placental proteins (marker) HPL, β-HCG, and CEA. Of these patients, 72 per cent showed abnormally high HPL, and 45 per cent showed high plasma β-HCG, while 52 per cent showed high plasma CEA (Fig. 1).

Twenty of these patients with epithelial tumors were studied during therapy. There was a correlation between the marker and the course of the disease in some patients, but, in some, there was a discordance, where clinical deterioration was associated with a fall rather than a rise in plasma marker.

The most likely explanation for this discordance is inhibition of marker production or secretion but not tumor growth by the chemotherapeutic agent or radiotherapy. This could occur if the tumors were comprised of a heterogenous population of marker- and non–marker-producing cells with different growth rates and variable susceptibility to the therapy.[11, 12] An alternative explanation of discordance may be that the tumor volume may lag behind hormone production, changing the number of proliferative cells.[13] It is also possible that the drug might be responsible for a change in the metabolic clearance rate of secreted marker without necessarily causing any change in the marker-producing cells themselves. In addition, in view of the increasing recognition of instances of protein heterogeneity,[14, 15] the theoretical possibility of drug-induced shifts in the synthesis of the marker to substances less well measured in the assay employed could be raised. The high level of the marker in some of the patients studied, in absence of evidence of clinical disease, may be due to the presence of an incipient disease.

The placental proteins (HPL and β-HCG) are normally undetectable in the circulation even when sensitive methods (permitting detection of as little as 1 ng. per milliliter are employed. However, CEA can be elevated in certain cases of nonneoplastic disease,[16] whereas such cases have yet to be documented for the placental protein markers.[17, 18]

From our study, it appears that measurement of biochemical markers in ovarian cancer may be of scientific value, but, from our data, this measurement does not appear to be useful in assessing the clinical status of the patient or the effect of therapy.

We wish to express our deep appreciation to Dr. Henry G. Friesen, University of Manitoba, Winnipeg, Manitoba, Canada, for the human placental lactogen (HPL); to Hoffmann-La Roche Inc., Roche Park, Nutley, New Jersey 07110, for the carcinoembryonic antigen (CEA); and to the National Institutes of Health for the chorionic gonadotropin (β-HCG) and antibody. We also wish to express our thanks to Jean Britton and Pamela Crosley for their excellent technical assistance.

REFERENCES

1. Lipsett, M. B.: Cancer Res. **25:** 1068, 1965.
2. Liddle, G. W., Nicholson, W. E., Island, D. P., Orth, D. N., Abe, K., and Lowder, S. C.: Recent Prog. Horm. Res. **25:** 283, 1969.

3. Rosen, S. W., Becker, C. E., Schaff, S., Easton, J., and Gluck, M. C., N. Engl. J. Med. **279:** 640, 1968.
4. Rudnick, P., and Odell, W. D.: N. Engl. J. Med. **284:** 405, 1971.
5. Gerfo, P. L., Krupey, J., and Hansen, H. J.: N. Engl. J. Med. **285:** 138, 1971.
6. Weintraub, B. D., and Rosen, S. W.: J. Clin. Endocrinol. Metab. **32:** 94, 1971.
7. Braunstein, G. C., Vaitukaitis, J. I., Carbone, P. P., and Ross, G. T.: Ann. Intern. Med. **78:** 39, 1973.
8. Samaan, N. A., Yen, S. C. C., Friesen, H., and Pearson, O. H.: J. Clin. Endocrinol. Metab. **26:** 1303, 1966.
9. Vaitukatis, J. H., Braunstein, G. D., and Ross, G. T.: Am. J. Obstet. Gynecol. **113:** 751, 1972.
10. Thompson, D. M. P., Krupey, J., Freedman, S. O., and Gold, P.: Proc. Natl. Acad. Sci. U. S. A. **64:** 161, 1969.
11. Braunstein, G. D., McIntire, K. R., and Waldmann, T. A.: Cancer **31:** 1065, 1973.
12. Hakansson, L., and Trope, C.: Acta Pathol. Microbiol. Scand. (A) **82:** 35, 1974.
13. Bagshawe, K. D.: Br. J. Cancer **22:** 698, 1968.
14. Li, M. C.: Ann. Intern. Med. **74:** 102, 1971.
15. Franchimont, P., Gaspard, U., Reuter, A., and Heynen, G.: Clin. Endocrinol. **1:** 315, 1972.
16. Moore, T. L., Kupchik, H. Z., Marcon, N., and Zamchek, N.: Am. J. Dig. Dis. **16:** 1, 1971.
17. Rosen, S. W., Weintraub, B. D., Vaitukaitis, J. L., Sussman, H. H., Hershman, J. M., and Miggia, F. M.: Ann. Intern. Med. **82:** 71, 1975.
18. Weintraub, B. D., and Rosen, S. W.: Metabolism **22:** 1119, 1973.

Dysgerminoma of the ovary: Radiation therapy for recurrence and metastases

MUHAMMAD ALI AFRIDI, M.D.
VITUNE VONGTAMA, M.D.
YOSHIAKI TSUKADA, M.D.
M. STEVEN PIVER, M.D., F.A.C.O.G.
Buffalo, New York

Nine cases of dysgerminoma are reported. Five patients developed recurrence of disease in either the pelvis or metastatic sites including the lung and brain. The metastatic disease was controlled by a radiation dose of 2,000 to 3,000 rads during three to four weeks in four of the patients. The excellent response of dysgerminoma to radiation warrants an optimistic prognosis and vigilant follow-up since metastatic disease can be controlled by moderate radiation doses.

DYSGERMINOMA belongs to the group of germ cell tumors of the ovary. It is a relatively rare tumor which occurs mostly in young women under the age of 30 years. The incidence of dysgerminoma has been described as 2.6 to 5.0 per cent of all primary malignant ovarian neoplasms.[1, 2] It usually occurs in a pure form, although it has also been found mixed with other germ cell tumors.[3, 4]

Dysgerminoma is a malignant tumor which spreads by direct extension and disseminates early via the lymphatics to the para-aortic, mediastinal, and left supraclavicular lymph nodes. Hematogenous spread to the liver and lungs occurs in the advanced stages of the disease.

The over-all survival rate varies widely among the different series. Mueller and associates[2] reported a five-year survival rate of 27.3 per cent. Kottmeier[5] reports a survival rate of 67.2 per cent. Thoeny and colleagues[6] reported a five-year cure rate of 75 per cent; Assadourian and Taylor[7] in a review of 105 cases reported a five-year survival rate of 86 per cent.

Analysis of nine cases of dysgerminoma treated at Roswell Park Memorial Institute between 1940 and 1974 is presented in this paper.

From the Departments of Radiation Medicine, Pathology, and Gynecology, Roswell Park Memorial Institute.

Received for publication September 25, 1975.

Revised January 26, 1976.

Accepted February 24, 1976.

Reprint requests: Dr. M. A. Afridi, Radiation Medicine Department, Roswell Park Memorial Institute, 666 Elm St., Buffalo, New York 14263.

Material and methods

There were 15 cases with a chart diagnosis of dysgerminoma in which the patient was admitted to Roswell Park Memorial Institute between 1940 and 1974. The histologic material from these cases was reviewed.

Six of the 15 cases were excluded after review of histologic material. The remaining nine cases were accepted as pure dysgerminomas.

Clinical features. All nine patients were less than 30 years of age. The youngest patient was 11 years old, and the median age was 17 years. The most common presenting symptom was abdominal mass or enlargement noted by the patient (in five cases). Abdominal pain was present in four patients, and two patients had menorrhagia. Examination revealed a palpable abdominal mass in six patients and an adnexal mass in three patients.

Operative findings and staging. Eight of the nine patients had an initial operative procedure performed before being referred to this Institute. The right ovary only was involved in five cases, the left was involved in two, and both ovaries were involved in two. The size of the primary tumor varied from 9 to 25 cm.

The distribution of the nine patients according to the extent of the disease at the time of initial diagnosis is given in Table I (staging system of the International Federation of Gynecology and Obstetrics). Seven patients had Stage IIA or less disease, and one patient each had Stage IIB and III disease, respectively. At the time of referral to this Institute, only two patients were still in Stage IIA or less, while the remaining five had developed recurrence and/or metastases.

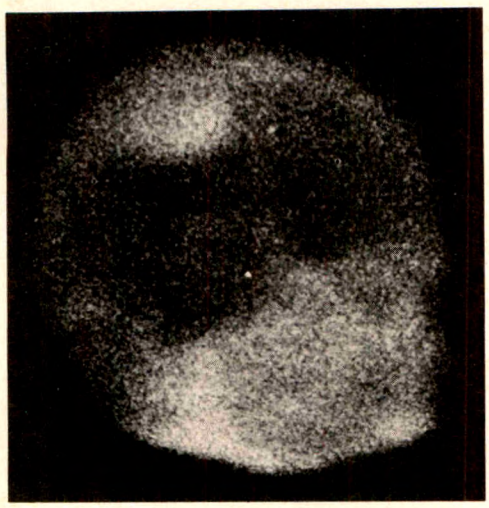


Fig. 1A. Case No. 4. Right lateral view of brain scan before irradiation showing abnormal uptake in right parietal lobe.

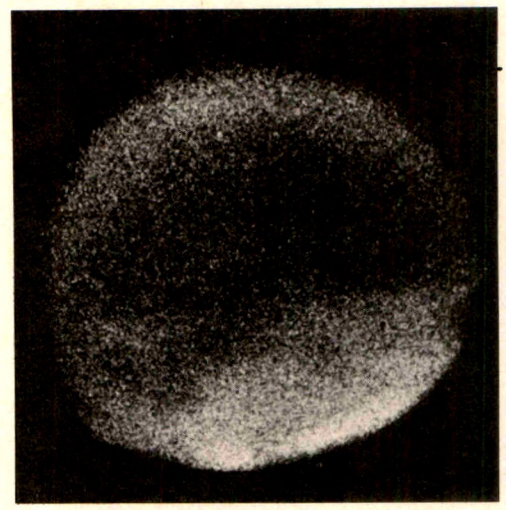


Fig. 1B. Case No. 4. Right lateral view of brain scan after irradiation (3,000 rads).

The distribution of these recurrences by site is shown in Table II.

Treatment and results.

Stages I and IIA (Table III). Of the seven patients with Stage I or IIA disease, two patients with bilateral tumors underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy as the initial operative procedure while the remaining five had unilateral salpingo-oophorectomy. Only two patients received postoperative pelvic radiation therapy as part of the initial treatment. Both of them developed distant metastases outside the irradiated field. As mentioned above, five of the seven patients developed recurrence and/or distant metastases. These recurrences and/or metastases were treated by radiation therapy. Most of the cases were treated with megavoltage machines such as the cobalt 60 and 6 MeV. x-ray linear accelerator. All radiation doses were calculated at midplane. No correction factor was used for the decreased lung absorption in patients who received pulmonary irradiation.

The pelvic and para-aortic disease was usually treated with anterior and posterior whole-abdomen fields with 2,000 to 3,000 rads delivered in four to six weeks followed by a booster dose of 1,000 to 1,500 rads in one to two weeks to an inverted Y or pelvic field. The mediastinal and supraclavicular areas received an average tumor dose of 2,000 to 3,000 rads in two to four weeks. Two patients with lung metastases were given 2,000 rads in three weeks to both lungs and mediastinum. The lung lesions showed a good response with complete disappearance of tumor on chest x-ray films.

The third patient received 1,500 rads in three weeks to the whole chest. Partial regression of the metastatic nodules in both lungs occurred, but six months later

Table I. Staging at initial diagnosis

Stage I			*Stage II*		
A	*B*	*C*	*A*	*B*	*Stage III*
2	2	1	2	1	1

Stage I and IIA = 7. Stage IIB and III = 2.

Table II. Site of recurrences

Site	*No.*
Para-aortic nodes	4
Lungs	3
Pelvis	3
Hilum and mediastinum	2
Liver	2
Brain	1

the patient died from progressive disease involving the liver, abdomen, and lungs. Two patients are described below in detail to illustrate the effectiveness of radiation therapy in treating metastatic sites.

Case reports

Case No. 4. A 21-year-old white woman had total abdominal hysterectomy and bilateral salpingo-oophorectomy in June, 1973, for a 25 cm. left ovarian mass which proved to be dysgerminoma. The right ovary was also involved. Postoperatively, she received a midline dose of 3,000 rads to the pelvis in three weeks on the cobalt 60 machine. In December, 1973, the tumor recurred in the para-aortic nodes. A 16 by 16 cm. retroperitoneal mass was found extending from the level of the first to the fourth lumbar vertebra and surrounding the left kidney and major blood vessels. Three thousand rads were given to the whole abdomen in six weeks. The mediastinum and left supraclavicular

Table III. Dysgerminoma: Stages I and IIA

Case No.	*Age of patient*	*Stage*	*Size and site of tumor*	*Initial treatment*		*Recurrence or metastasis*
				Operation	*Postoperative irradiation*	
1	23	IA	14 cm., RT	SO	3,700 rads in 5 weeks to pelvis	1. Para-aortic nodes 2. Mediastinum and left supraclavicular area
2	29	IA	10 cm., RT	SO	None	None
3	15	IB	20 cm., RT 4 cm., LT	TAH + BSO	None	None
4	21	IB	25 cm., LT 5 cm., RT	TAH + BSO	3,000 rads in 3 weeks to pelvis	1. Para-aortic nodes 2. Lungs 3. Brain
5	11	IC	12 cm., RT; 4,000 c.c. bloody ascites	SO	None	1. Pelvis and para-aortic nodes 2. Lungs and hilum
6	17	IIA	17 cm., RT	SO	None	1. Pelvis, omentum, abdomen, and peritoneum 2. Liver
7	13	IIA	17 cm., RT	SO	None	1. Pelvis and para-aortic nodes 2. Lungs 3. Liver

RT = Right ovary; LT = left ovary; SO = salpingo-oophorectomy; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; NED = no evidence of disease.

area were treated electively with 2,000 rads in two weeks.

In August, 1974, she developed bilateral lung metastases. Two thousand rads in three weeks were given to the whole chest with complete regression of metastatic nodules. In January, 1975, she developed headache, low-grade papilledema, and weakness of the left upper and lower extremities with marked hyperflexion. A brain scan was positive in the right parietal lobe (Fig. 1A). The patient received 2,000 rads to the whole brain in two weeks followed by 1,000 rads in one week to the tumor-bearing area. At the end of the treatment course, she had completely recovered from neurological symptoms and signs, except for minimal left-foot weakness. Brain scan repeated three months later was normal (Fig. 1B). The patient has remained well for six months following radiation to the brain with no apparent sign of disease.

Case No. 6. A 17-year-old white female subject underwent a laparotomy in April, 1970, because of a lower abdominal mass. A right salpingo-oophorectomy and removal of a 17 cm. mass in the right adnexa were carried out. She did not receive any radiation therapy. In September, 1970, the patient developed recurrent masses in the pelvis and the omentum. The whole abdomen was given 2,100 rads, and the pelvis received an additional booster dose of 1,400 rads. The liver was shielded. In December, 1971, a liver scan revealed a large space occupied by lesions (Fig. 2A). A needle biopsy was positive for dysgerminoma. A total dose of 2,500 rads was given to the whole liver in four weeks. The liver returned to normal size. Liver scans repeated

Treatment for recurrence or metastasis	Present status	Survival in years: From diagnosis	Survival in years: From last treatment
1. 4,000 rads in 4 weeks 2. 3,000 rads in 3 weeks	NED	19	18
None	NED	11	11
None	NED	8	8
1. 3,000 rads in 6 weeks to whole abdomen + 2,000 rads in 3 weeks to mediastinum and left neck 2. 2,000 rads in 3 weeks to whole chest 3. 3,000 rads in 3 weeks	NED	2	½
1. 2,000 rads in 4 weeks to whole abdomen + 3,000 rads to para-aortic nodes 2. 2,000 rads to whole chest + 1,000 rads as boost to mediastinum	NED	4	1
1. 2,100 rads in 4 weeks to whole abdomen + 1,400 rads in 1 week to pelvis 2. 2,500 rads in 4 weeks	NED	5	3½
1. 3,000 rads in 4 weeks to whole abdomen 2. 1,500 rads in 3 weeks 3. 1,800 rads in 3 weeks	Died from disease	2	—

at the end of treatment and one and a half years later were normal (Fig. 2B). The patient is alive and well three and a half years later.

Results in the above group are shown in Table III. Six of the seven patients are alive and free from disease at the time of the last follow-up. Four patients have survived 19, 11, eight, and five years from diagnosis (Case Nos. 1, 2, 3, and 6, respectively). The other two patients (Case Nos. 4 and 5) are alive and free from disease two and four years from initial diagnosis, although follow-up periods after the last treatment are only six months and one year, respectively.

Four of the five patients who developed distant metastasis are alive and well after radiation therapy to metastatic sites.

Stages IIB and III. There were two patients in this group. One patient with Stage IIB disease had a 9 cm. tumor involving the left ovary, extending to the left pelvic wall, and surrounding the left ureter. Partial resection and bilateral salpingo-oophorectomy were done followed by radiation to the pelvis and lower abdomen with a midline dose of 3,000 rads in three weeks, on the megavoltage unit. The patient is alive with no evidence of disease eight years later.

The second patient was found to have a 15 cm. tumor of the right ovary at laparotomy. The omentum and para-aortic nodes were also involved, with the tumor extending around both kidneys (Stage III). Bilateral salpingo-oophorectomy and partial resection of the para-aortic masses were carried out. Postoperatively, 2,500 rads were delivered in five weeks to the whole abdomen, and an additional 1,000 rads was given to the pelvis in 10 days.

This patient is alive and free from disease after 10 years.

Comment

Surgical removal of the primary tumor is the initial treatment of choice in all cases of dysgerminoma. The extent of operation and the use of postoperative radiation therapy in young patients with unilateral encapsulated tumors without evidence of spread (Stage IA) is controversial. Assadourian and Taylor[7] recommend only unilateral salpingo-oophorectomy in such cases. Kottmeier[5] suggests unilateral salpingo-oophorectomy followed by radiation to the area of growth and the retroperitoneal lymph nodes. Pedowitz and associates[8] and Thoeny and colleagues[6] recommend total extirpation of the internal female genitals followed by postoperative radiation therapy to the pelvis and para-aortic nodes in all cases, because of high recurrence rates (30 to 50 per cent).

The value of radiation therapy in patients with disease beyond Stage IA or with recurrences or distant metastases is not disputed. In our series, of the 7 patients with Stage IIA or less disease who apparently had total resection of the tumor at the time of initial diagnosis, five developed recurrences. Two of these five patients had postoperative pelvic irradiation, and, significantly, recurrences only developed above the pelvis. The other three patients who did not receive postoperative radiation therapy had recurrences both in the pelvis and above the pelvis. The mode of spread was almost typical, i.e., the disease spread from the pelvis to the para-aortic nodes and later appeared in the mediastinum and lung. Treatment of the pelvic recurrences and distant metastases with radiation therapy gave good results. Four of these five patients are alive and well. The two patients with Stages IIB and III disease are also alive and well after partial resection

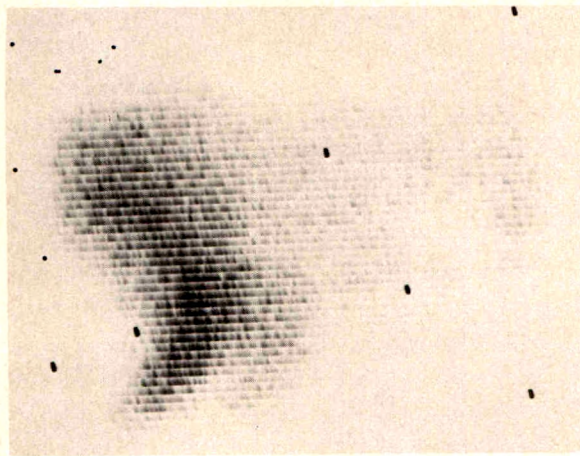


Fig. 2A. Case No. 6. Anterior view of liver scan, before irradiation, showing space occupying lesion in right lobe.

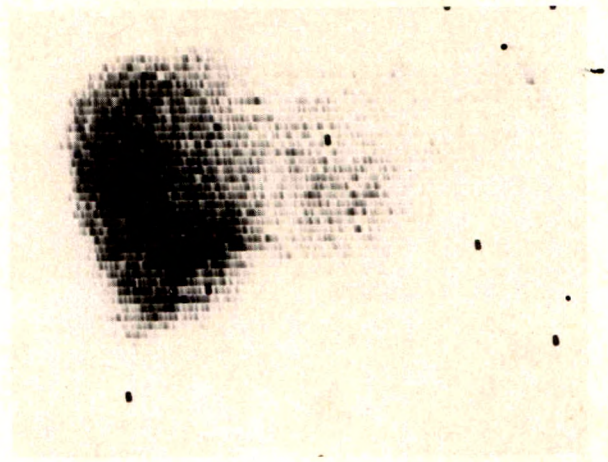


Fig. 2B. Case No. 6. Anterior view of liver scan after irradiation (2,500 rads).

of the tumor mass followed by radiation therapy. Similarly good results even in advanced stages have been reported by other authors.[9–11]

Therefore, it is our policy that in all stages of dysgerminoma of the ovary total abdominal hysterectomy and bilateral salpingo-oophorectomy and resection of as much tumor mass as possible must be carried out. In Stages IB and IIA, this is followed by 3,000 rads in three to four weeks to the pelvis and para-aortic nodes. If the para-aortic nodes are positive at laparotomy, then the mediastinum and left supraclavicular nodes are electively treated with 2,500 rads in three weeks. In Stages IC, IIB, and III and some cases of Stage IV the whole abdomen is treated with 3,000 rads in six weeks followed by a booster dose of 1,000 to 1,500 rads in two weeks to the pelvis and para-aortic nodes.

Conservative therapy in the form of unilateral salpingo-oophorectomy is carried out in some patients with Stage IA disease who are young and wish to have children. The other ovary is bivalved and biopsied; para-aortic nodes are carefully palpated during laparotomy, and suspicious nodes are biopsied. Pelvic and paracolic washings are also obtained for cytology. If the para-aortic nodes and the washings are negative for malignant cells, then the patient is closely followed after the unilateral salpingo-oophorectomy.

Conclusion

As demonstrated in this series, dysgerminoma is both a radiosensitive and a radiocurable tumor, and, even with extensive metastases, prolonged periods of survival with apparent cures can be obtained. Awareness of this potential curability of dysgerminoma and institution of adequate radiotherapy to the metastatic sites can improve results in these advanced cases.

REFERENCES

1. Burns, B. C., Jr., Rutledge, F. N., Smith, J. P., and Delclos, L.: Management of ovarian carcinoma, surgery, irradiation, and chemotherapy, Am. J. Obstet. Gynecol. **98:** 374, 1967.
2. Mueller, C. W., Topkins, P., and Lapp, W. A.: Dysgerminoma of ovary. An analysis of 427 cases, Am. J. Obstet. Gynecol. **60:** 153, 1950.
3. Neigus, I.: Ovarian dysgerminoma with chorioepithelioma, Am. J. Obstet. Gynecol. **69:** 833, 1955.
4. Larson, N. E., Dockerty, M. B., and Pratt, J. H.: Primary mixed choriocarcinoma and dysgerminoma of ovary, Mayo Clin. Proc. **33:** 431, 1958.
5. Kottmeier, H. L.: Ovarian cancer with special regard to radiotherapy, Am. J. Roentgenol. Radium Ther. Nucl. Med. **3:** 417, 1971.
6. Thoeny, R. H., Dockerty, M. B., Hunt, A. B., and Childs, D. S.: A study of ovarian dysgerminoma with emphasis on the role of radiation therapy, Surg. Gynecol. Obstet. **113:** 692, 1961.
7. Assadourian, L. A., and Taylor, H. B.: Dysgerminoma. An analysis of 105 cases, Obstet. Gynecol. **33:** 370, 1969.
8. Pedowitz, P., Felmus, L. B., and Grayzel, D. M.: Dysgerminoma of the ovary. Prognosis and treatment, Am. J. Obstet. Gynecol **70:** 1284, 1955.
9. Brody, S.: Clinical aspects of dysgerminoma of ovary, Acta Radiol. **56:** 209, 1961.
10. Talerman, A., Huyzinga, W. T., and Kuipers, T.: Dysgerminoma—Clinicopathologic study of 22 cases, Obstet. Gynecol. **41:** 137, 1973.
11. Delclos, L., and Smith, J. P.: Tumors of ovary, *in* Fletcher, G. H., editor: Textbook of Radiotherapy, Philadelphia, 1973, Lea & Febiger, Publishers, p. 700.



ıARY KNOWS FETAL MONITORS NSIDE OUT,

nd their importance to you and your patient.

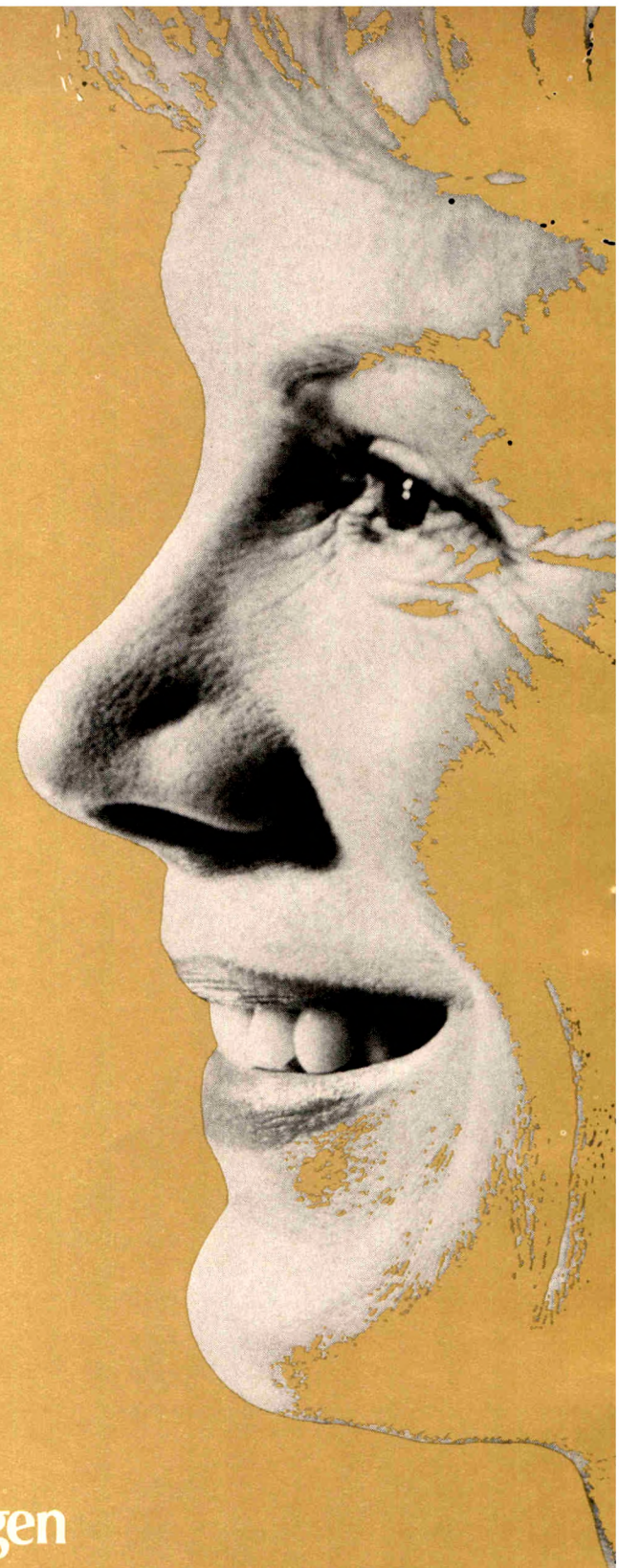
ıry Viski, one of many fine people at Corometrics, s thirty years electronics wiring experience. She's en with us since we began. Through our in-house ucation program, Mary learned the value of fetal ɔnitoring to others. We know it's important to ve people like Mary who know what they're doing. ıd you can rely upon us, because we rely upon Mary.

FOR MORE INFORMATION ON PERINATAL INSTRUMENTATION, CONTACT:

COROMETRICS MEDICAL SYSTEMS, INC.
2 Barnes Industrial Park Road
Wallingford, Connecticut U.S.A. 06492
Tel: (203) 265-5631 Telex: 940-403

COPYRIGHT ©1975

Estrogen replacement therapy moves forward



the major human estrogen micronized for oral effectiveness

Estrace®
(estradiol)

1-mg. and 2-mg. scored tablets

- not esterified, not conjugated
- estradiol...the active estrogen at the cellular level

from Mead Johnson

overall, 95% of patients studied gained adequate or complete relief of their symptoms[1]

Estrace (estradiol) was given to 369 estrogen-deficient women for periods ranging up to a year or more (average of six months); 319 of these women received an initial dosage of 1 or 2 mg. per day and were evaluated for efficacy. *Complete disappearance* of hot flushes was experienced by 227 (76%) of 298 women, of sweating by 131 (80%) of 164 women, of tingling by 62 (94%) of 66 women, and of genital atrophy by 44 (88%) of 50 women. In general, 95% of the patients evaluated experienced either adequate or complete relief of their symptoms. Remarkably, in 77% of the patients, symptoms were controlled without need to adjust the initial dosage—usually 2 mg. daily. (Dosage after adjustment ranged from 1 mg. to 3 or 4 mg. a day.)[1]

cyclic therapy recommended

Recently, published reports of retrospective human data have emphasized that patients using estrogens may have an associated increased risk of endometrial cancer. This information makes cyclic rather than continuous estrogen replacement therapy even more prudent. (See brief summary.)

With Estrace, treatment should be initiated with a dose of 1 or 2 mg. daily and then adjusted to the lowest dose possible still maintaining the relief of symptoms. The usual regimen for cyclic administration of Estrace is three weeks on drug, followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4–6 days) to prevent recurrence of menopausal symptoms.

estradiol... orally effective

The technique of micronization has opened up the oral route to natural human estrogen replacement with Estrace. Reduced particle size of the estradiol in Estrace makes effective gastrointestinal absorption possible. Onset of action is rapid, with marked increases in levels of circulating estradiol and estrone; concomitant decreases in serum concentrations of FSH and LH are sustained over a 24-hour period.[2]

Because estradiol can be assayed in plasma, Estrace can provide objective[2] as well as clinical evidence[1] of ready availability and biologic activity.

well accepted by patients[1]

In the 369 patients previously described, the incidence of estrogen-induced side effects with Estrace was relatively low. Incidence of nausea was remarkably low—only 2% of patients before dosage adjustment. Some patients who had complained of this problem while on conjugated equine estrogens reported its complete disappearance on changing to Estrace. Whereas before dosage adjustment 24% experienced breast tenderness, 31% edema, 18% (of 151 with intact uteri) bleeding, and 4% weight gain, only about 2% of the 369 patients dropped out because of side effects.[1]

long-term therapy should be monitored

A few instances of significant gynecologic disease became apparent during clinical investigations.[1] Endometrial hyperplasia was discovered in seven patients, all of whom had previously received estrogen therapy for one to three years prior to entering the study. One patient was reported to have carcinoma *in situ* and another showed adenocarcinoma of the endometrium. In clinical practice, the physician should be alerted to the potential of thrombotic disorders and be prepared to discontinue medication immediately if they occur. Because of variations in normal endogenous hormone production, certain patients may exhibit signs of excessive estrogenic stimulation. Adverse reactions generally associated with estrogen administration may occur and these are listed in the brief summary. Prior to initiation of treatment with Estrace or any other estrogenic preparation, an adequate physical examination should be given.

References

1. Callantine, M.R., *et al.*: Micronized 17β-estradiol for oral estrogen therapy in menopausal women, Obstet. Gynecol. *46*:37–41 (July) 1975.
2. Yen, S.S.C., *et al.*: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β-estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. *40*:518–521 (March) 1975.

For Brief Summary, please see following page.

Estrogen replacement therapy moves forward...

Estrace® (estradiol)

the major human estrogen micronized for oral effectiveness



Indications: Estrace® (17β-Estradiol) is indicated for relief of endogenous estrogen deficiency and associated menopausal symptoms.

Contraindications: Estrace® is contraindicated in patients with 1) markedly impaired liver function; 2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible; 3) known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium; 4) undiagnosed abnormal genital bleeding; 5) thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions; and 6) pregnancy.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen medication should be stopped. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

Adverse Reactions: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis). The following adverse reactions are known to occur in patients receiving estrogens: nausea, vomiting, anorexia, gastrointestinal symptoms (such as abdominal cramps or bloating), edema, breakthrough bleeding, spotting or withdrawal bleeding, breast tenderness and enlargement, change in body weight (increase or decrease), headache, increased cervical mucus, allergic rash, loss of libido and gynecomastia in the male, reactivation of endometriosis, aggravation of migraine headaches, hepatic cutaneous porphyria becoming manifest, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, cystitis-like syndrome, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, possible diminution in lactation when given immediately post-partum, irritability, and malaise.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than nonusers to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study. In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients. Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued. It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Childbearing Age, Brit. Med. J., 2:193-199, 1968. (3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969. (5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970. (6) Herbst, et al. — Adenocarcinoma of the Vagina — New England Journal of Medicine, Vol. 284, Number 16 (April 22, 1971).

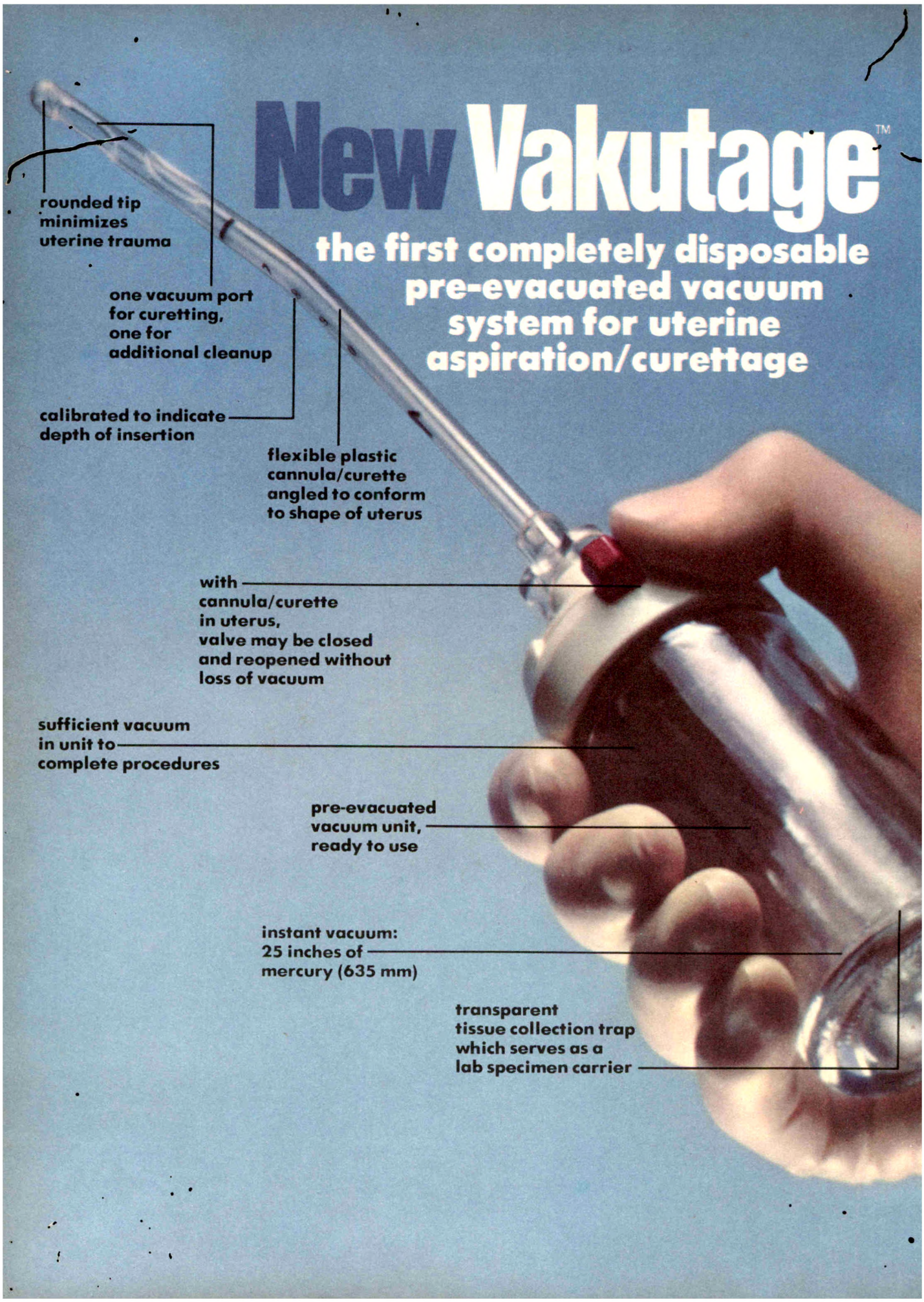
Dosage and Administration: Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol. Dosage may be adjusted to control the presenting symptoms depending on the response of the individual patient; the minimal effective dose for maintenance therapy should be determined by titration. To avoid continuous stimulation of the reproductive tract and breasts, cyclic therapy is recommended. The usual regimen consists of three weeks on drug followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4-6 days) to prevent recurrence of menopausal symptoms. Withdrawal bleeding of unusual amount or duration should be investigated.

How Supplied: Estrace® 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace® 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. MJL 5-4127


The end of pumps, plugs, noise,
hoses, cords and cannula/curette cleanup.
Now, a new era
in uterine aspiration/curettage.


New Vakutage™
the first completely disposable pre-evacuated vacuum system for uterine aspiration/curettage
rounded tip minimizes uterine trauma
one vacuum port for curetting, one for additional cleanup
calibrated to indicate depth of insertion
flexible plastic cannula/curette angled to conform to shape of uterus
with cannula/curette in uterus, valve may be closed and reopened without loss of vacuum
sufficient vacuum in unit to complete procedures
pre-evacuated vacuum unit, ready to use
instant vacuum: 25 inches of mercury (635 mm)
transparent tissue collection trap which serves as a lab specimen carrier

Designed for maximum efficiency in endometrial biopsy, menstrual induction, and uterine curettage

At last, the simplicity of Vakutage makes office aspiration/curettage truly practical.

With Vakutage, there is no need for electrical or mechanical vacuum sources. No aspiration or curettage instruments to sterilize before procedures or clean up afterward.

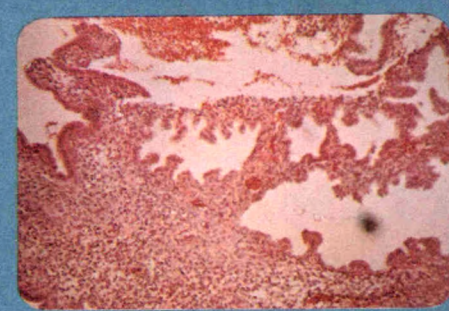
Vakutage is unobtrusive and completely silent when in use—a compact instrument compared to vacuum sources of conventional aspiration equipment.

With Vakutage, local anesthesia and cervical dilatation are usually unnecessary for endometrial biopsy or menstrual induction.

Provides reliable tissue specimens

Unlike the washout technique, biopsy with Vakutage provides intact tissue, not suspended cells.

Pathologists involved in clinical trials found Vakutage biopsy specimens to be equal or superior to those obtained by conventional metal curettes.



Early secretory endometrium



Adenocarcinoma of endometrium

_____ Please send more information on Vakutage.™

_____ I would like a demonstration of the Vakutage™ system. Please have the Warner/Chilcott Sales Representative call.

Doctor _____
(Please print)

Address _____

City _____ State _____ Zip _____

Primary Specialty _____

Signature _____ M.D.

Vakutage proved simple, safe and reliable in 770 procedures performed by eight clinical investigators*



Tissue sufficient for diagnosis obtained in 92% of endometrial biopsies.*
Local anesthesia and cervical dilatation were rarely used. Incidence of transient cramping, pain, spasm, or other side effects was low. Adequate vacuum reported for large majority of Vakutage units.† Mechanical problems—clogged cannula/curette or tight valve—were minimal.

Endometrial lining efficiently aspirated in 90% of menstrual inductions.*
No operative or postoperative complications encountered in patients with menses delayed up to 28 days. Adequate vacuum reported for large majority of Vakutage units.† Trouble-free operation of Vakutage unit reported by all investigators in most cases.

Tissue adequate for diagnosis removed in 98% of D & C's.*
About 80% of the procedures were performed in the physician's office. Routine follow-up with metal instrument curettage or vacuum aspiration yielded no "missed" tissue. No operative complications, and only one case of mild postoperative bleeding for five days. Adequate vacuum in large majority of Vakutage units.†

Warner/Chilcott
Division,
Warner-Lambert Company
Morris Plains,
New Jersey 07950

*Data on file at Warner/Chilcott Medical Department.
†In rare instances of inadequate vacuum, the used collection unit can be replaced by another unused one, without removing cannula/curette from uterus.

Printed in U.S.A. V-GP-51 May, 1976.

First Class
Permit #2
Morris Plains
New Jersey

BUSINESS REPLY MAIL
NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

Postage will be paid by:

Warner/Chilcott
201 Tabor Road
Morris Plains, New Jersey 07950

Attention: Vakutage™



Vakutage™
Compact. Convenient. Self-contained.

OBSTETRICS

Maternal and fetal effects of lumbar epidural analgesia for labor and delivery in patients with gestational hypertension

FRANCIS M. JAMES III. M.D.
PAUL DAVIES, PH.D.
Birmingham, England

The effects of continuous lumbar epidural analgesia for labor and delivery were studied in 20 women with gestational hypertension. Maternal hemodynamics, renal function, acid-base, and blood gas findings were examined together with newborn Apgar scores and umbilical vessel blood gas and acid-base values. Minimal change occurred in maternal renal function and hemodynamics. Maternal and newborn acid-base and blood gas findings were comparable to those of normotensive control subjects also receiving epidural analgesia. Apgar scores in both groups of subjects were good. Continuous epidural analgesia is recommended as a useful form of therapy in the management of labor and delivery in women with gestational hypertension.

THE DEVELOPMENT of hypertension during pregnancy continues to be a major obstetric problem. Uniform opinion on how to manage patients with gestational hypertension, pre-eclampsia, or eclampsia during labor and delivery is lacking.

Continuous epidural analgesia for labor and delivery of pre-eclamptic patients has been recommended by several authorities.[1-3] Belief in improved renal function via relief of renal vasospasm, better control of maternal blood pressure by sympathetic blockade plus excellent analgesia, and less infant depression through decreased maternal sedative and narcotic requirements form the basis of such recommendations. In opposition, many clinicians believe conduction analgesia is contraindicated in pre-eclamptic and eclamptic women for decreased blood volume might make them more vulnerable to hypotension.

In this study we investigated the effects of continuous lumbar epidural analgesia on maternal hemodynamics, renal function, and acid-base balance in patients with gestational hypertension. Fetal observations consisted of umbilical cord acid-base and blood gas findings plus Apgar scores.

From the Department of Anaesthetics of the Birmingham Maternity Hospital, the Department of Anesthesia of the Bowman Gray School of Medicine, and the Department of Mathmatical Statistics of the University of Birmingham.

Received for publication October 21, 1975.

Revised January 9, 1976.

Accepted February 17, 1976.

Reprint requests: Francis M. James, III. M.D. Department of Anesthesia of the Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103.

Methods

Twenty pregnant women with gestational hypertension were studied. To qualify for the study maternal blood pressures of at least 140/90 had to be present on two or more occasions more than 6 hours apart. Although not prerequisite for inclusion in the study, the presence or absence of edema and proteinuria was noted. The night prior to induction of labor the study procedures were explained to the patient and permission obtained to perform them. On admission to the delivery suite patients assumed a lateral position in bed and preinduction blood pressure and pulse were recorded, a urinary catheter was placed in the bladder,

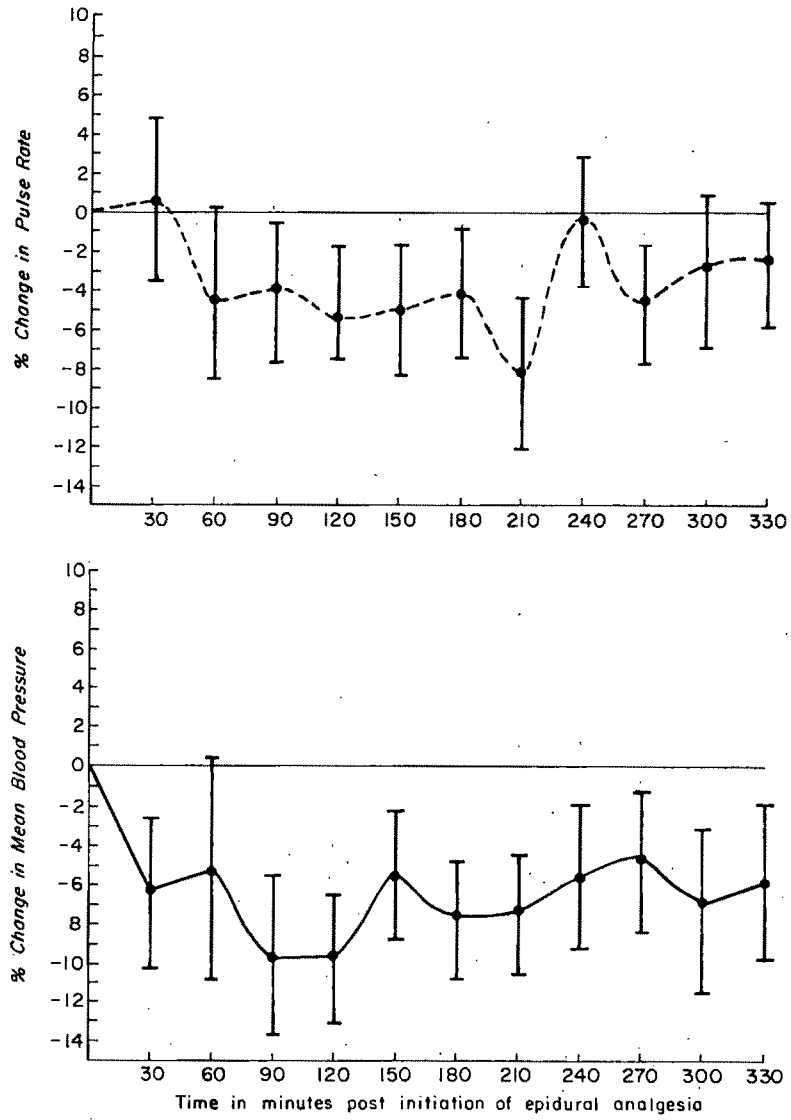


Fig. 1. Changes in blood pressure and pulse rate with epidural analgesia.

and a plastic catheter positioned in a peripheral vein. The latter was subsequently used for the administration of oxytocin by constant infusion (Meltee) pump. Blood was withdrawn through this catheter for determination of serum creatinine and blood urea nitrogen. A central venous pressure catheter was placed via the basilic vein and a baseline reading recorded. Subsequently, 5 per cent dextrose in water was infused at 50 to 70 ml. per hour via the CVP line and baseline blood gas and acid-base determinations were carried out on a radial artery specimen. Finally, a catheter was placed in the lumbar epidural space. One hour after urinary catheterization and 5 minutes after the test dose of 2 ml. of 0.5 per cent lidocaine, 10 ml. of 0.5 per cent bupivacaine were injected into the lumbar epidural space. Patients were positioned in an upright sitting position for the initial 15 minutes after epidural injection to facilitate the onset of perineal analgesia for amniotomy. They were then maintained in a lateral tilt position throughout labor and delivery. Upon obtaining adequate analgesia amniotomy was performed and fetal ECG and maternal intrauterine pressures were monitored by intrauterine techniques. Urine output was measured for the hour prior to injection of bupivacaine into the epidural space and each hour thereafter. Each specimen was checked for protein and 5 ml. aliquots were saved for subsequent creatinine and sodium determinations for the calculation of creatinine clearance and sodium excretion. The sensory level of epidural analgesia was maintained at the eighth thoracic vertebra or above and the following measurements were made. Blood pressure and pulse were recorded

Table I. Characteristics of subjects studied

	Mean
Age (yr.)	26.5
Weight (Kg.)	80.3
Weight gain (Kg.)	13.7
Height (cm.)	161.8
Hemoglobin (Gm.)	12.5
Blood pressure (mm. Hg)	
Systolic	140.3
Diastolic	94.9
Mean	109.0
Central venous	
Pressure (cm. H_2O)	4.2
Blood urea nitrogen (mg./100 ml.)	18.2
Creatinine (mg./100 ml.)	0.747
	% of subjects
Proteinuria	100
Edema	75
	No. of subjects
Gravidity	
G1	12
G2	6
G3	1
G4	1

Table II. Urinary function in 17 subjects during 6 hours of epidural analgesia

	Creatinine clearance (ml./min.)		*Sodium excretion (mEq./hr.)*		*Urine output (ml./hr.)*	
	Mean	*S.E.*	*Mean*	*S.E.*	*Mean*	*S.E.*
Control hour, pre-epidural	104.2	12.6	5.48	0.95	69.0	15.8
Postepidural:						
Hour 1	115.2	14.3	6.27	0.95	74.2	16.6
2	95.6	15.8	4.53	0.73	80.8	15.8
3	85.3	15.7	4.18	0.55	59.9	11.1
4	78.1	8.8	4.29	0.97	48.1	11.1
5	84.4	18.1	4.82	1.19	53.7	16.5
6	88.5	14.6	4.10	0.94	43.4	9.8
Changes from pre-epidural control hour:*						
Hour 1	+11.0	19.2	+0.79	0.87	+5.2	13.1
2	−8.5	16.6	−0.95	0.74	+11.9	17.0
3	−18.8	18.4	−1.30	0.92	−9.1	17.7
4	−26.1	15.2	−1.19	0.92	−20.8	16.6
5	−19.8	24.1	−0.66	1.42	−15.3	21.0
6	−15.7	14.7	−1.38	0.80	−25.6	14.0

*None of these changes was statistically significant.

Table III. Duration of labor

Stage	*No. of subjects*	*Mean time in (min.)*	*S.E.*
I	17	400.3	37.4
II	16	44.7	6.2
III	16	4.9	0.6

every 10 minutes by an Arteriosonde 1217 and central venous pressure was determined every half hour. Maternal arterial blood gases were repeated when the cervix dilated to 5 to 8 cm. and at delivery. Maternal and umbilical cord blood gas and acid-base status were compared with those of six normal control patients who delivered vaginally under epidural analgesia.

Newborn observations included Apgar scores plus umbilical artery and vein blood gas and acid-base determinations at the time of delivery.

Results

Several important maternal factors are included in Table I. Sixty per cent of subjects were primigravidas and 70 per cent were less than 30 years old. All had edema and/or proteinuria prior to and during labor. Mean arterial blood pressure was elevated on admission to the delivery suite to 109 mm. Hg. Changes in maternal blood pressure with epidural analgesia were minimal (Fig. 1), although a mild decrease persisted until near delivery time. Despite this minimal fall there were notable occasions during which mental excitement resulted in transient sharp climbs in blood pressure. Preparation for vaginal examination, the entrance of a husband into the labor room, and the act of preparing to withdraw blood from the CVP line all were capable of causing blood pressure increases even with an epidural sensory level of the sixth to the eighth thoracic vertebra. Only one patient had a severe enough blood pressure decline to warrant vasopressor therapy. Her mean arterial pressure dropped 33 per cent in an upright sitting position 6 minutes after epidural injection and failed to respond to assumption of the left lateral position and rapid intravenous administration of 200 ml. of 5 per cent dextrose in water accompanied by a 7 cm. H_2O increase in CVP. Normal pressure returned after 30 mg. of ephedrine were given in 7.5 increments over 3 to 4 minutes. Approximately 8 hours later she required an additional 7.5 mg. dose of intravenous ephedrine following an epidural top up. Two other patients experienced moderate hypotension while in the initial sitting position but responded briskly to being placed in the left lateral position. Changes in maternal pulse were even less marked than those in blood pressure (Fig. 1), whereas central venous pressure was virtually unaffected with a 3.2 cm. H_2O maximum mean variation from an initial value of 4.2 cm. H_2O in 13 subjects.

No significant alteration occurred in creatinine clearance, sodium excretion, or urine output from the pre-epidural control hour throughout several hours of analgesia. Table II contains urinary function data for 17 patients for the first 6 hours of epidural analgesia. Three of 20 subjects delivered in less than 6 hours and

Table IV. Maternal artery and umbilical cord blood gases and acid-base findings in gestational hypertension and normal control subjects

	Gestational hypertension (n = 14)		*Control (n = 6)*		
	Mean	*S.E.*	*Mean*	*S.E.*	*Difference between groups*
Maternal artery before labor:					
O_2 (mm. Hg)	93.3	3.1	93.2	4.8	NS
pH	7.444	0.007	7.457	0.008	NS
CO_2 (mm. Hg)	28.5	1.2	28.2	0.7	NS
B.E. (mEq./L.)	−2.7	0.5	−2.3	0.3	NS
Maternal artery, delivery:					
O_2 (mm. Hg)	87.6	6.5	95.3	3.1	NS
pH	7.454	0.007	7.455	0.010	NS
CO_2 (mm. Hg)	26.5	0.8	27.8	1.4	NS
B.E. (mEq./L.)	−3.1	0.5	−2.7	0.5	NS
Umbilical artery:					
O_2 (mm. Hg)	19.5	1.5	21.5	2.1	NS
pH	7.304	0.020	7.305	0.017	NS
CO_2 (mm. Hg)	51.0	2.7	46.7	2.7	NS
B.E. (mEq./L.)	−2.6	1.1	−2.3	0.8	NS
Umbilical vein:					
O_2 (mm. Hg)	31.3	1.3	33.0	2.0	NS
pH	7.376	0.016	7.396	0.017	NS
CO_2 (mm. Hg)	39.8	1.3	36.2	2.0	NS
B.E. (mEq./L.)	−1.9	0.8	−2.3	0.9	NS

Table V. Apgar scores of newborn infants* delivered by vaginal route

	Apgar score			
	10	*8-9*	*5-7*	*0-4*
1 minute:				
Pre-eclampsia	0	14	2	0
Normal control	0	6	0	0
5 minutes:				
Pre-eclampsia	10	6	0	0
Normal control	5	1	0	0

*Number of gestational hypertension infants, 16; number of normal control infants, 6.

are not included. Though creatinine clearance and sodium excretion decrease from control levels after a first hour postepidural increase, the changes are not of statistical significance. Average hourly maternal urine formation was 55.7 ml. while 5 per cent dextrose in water was administered intravenously at 78 ml. per hour.

The duration of labor is illustrated in Table III. To avoid expending maternal effort from second-stage pushing all but one vaginal delivery were facilitated by outlet forceps. Maternal blood gas and acid-base levels changed little during the course of labor and delivery. Maternal and infant blood gases (Table IV) varied little from those of six normal control subjects also delivered under epidural analgesia. Apgar scores at 1 and 5 minutes for infants delivered by the vaginal route, though not quite as good as in control subjects, gave little evidence of depression (Table V). All newborn infants had uneventful postnatal nursery courses. Infants of preeclamptic mothers weighed 3.21 kilgrams and control infants weighed 3.33 kilograms.

Four of 20 patients were delivered by emergency cesarean section and Apgar scores, umbilical cord studies, and maternal delivery arterial blood gas and acid-base data from these are not included in this study. One section was for cephalopelvic disproportion, one for umbilical cord compression between pelvic brim and fetal head, the third for fetal distress thought to be caused by a tight nuchal cord, and the fourth for fetal distress and failure of labor to progress despite good uterine contractions. Two additional subjects were excluded from acid-base comparisons because of incomplete maternal data.

Comment

All subjects in this study qualified as gestational hypertensive patients. Some may have been preeclamptic but definite evidence of this was not obtained. None of them was hypertensive prior to 24 weeks' gestation and all had at least two blood pressure determinations of 140/90 mm. Hg or greater on two or more occasions further than 6 hours apart. Most had several pressure readings at this level or higher. All patients were hospitalized for rest several days prior to

induction because of elevated blood pressures. Most (75 per cent) of them had edema, but whether or not it was pathologic edema is unknown. Page[4] noted that generalized edema may or may not be present and should not be required for the diagnosis of pre-eclampsia. Edema of a nonpathologic type may occur in more than half of pregnant women at some time during pregnancy.[4] All of our patients had some degree of proteinuria prior to or during labor as determined by dip strips (Labstix). Quantitative determinations were not done on 24 hour specimens. Since proteinuria can be found in one-half to one-third of parturients,[5] its significance in our patients is not certain. Orthostatic proteinuria attributed to uterine pressure on renal veins may be present in 20 per cent of normal pregnant women.[6]

The mean blood pressure of our patients upon arrival in the labor room was elevated to 109 mm Hg. This might be attributed to anxiety in most subjects at this point despite careful explanation of the day's procedures on the preceding afternoon. The labile form of hypertension observed in pre-eclampsia-eclampsia is due to marked increase in vascular reactivity which causes generalized vasoconstriction.[4] In normal labor without epidural analgesia cardiac output, blood pressure, heart rate, and central venous pressure increase with uterine contractions.[7] Marx[7] stated that these changes are probably due to rapid expulsion of blood from the uterus into the circulation and the patient's reaction to pain, anxiety, and increased muscle activity in response to pain or bearing down. In patients with severe pre-eclampsia (160/110 mm. Hg) given epidural analgesia Moir and Willocks[2] noted decreases of more than 20 per cent in mean arterial blood pressures. Our failure to note such impressive decreases in blood pressure (Fig. 1) may have been due to the lesser severity of blood pressure elevation in our patients. The fact that our patients' pressures and pulses declined moderately rather than rising as is normal during labor can be explained by decreased peripheral resistance secondary to sympathetic blockade to at least the level of the eighth thoracic vertebra and a lack of pain during labor. The latter decreased patient anxiety markedly and obliterated somatic muscle activity in response to uterine contractions. Our failure to note increases in central venous pressure associated with uterine contractions is probably explained by similar mechanisms plus increased capability for pooling of blood in the lower extremities and splanchnic region in the presence of sympathetic blockade. Patients were kept in a lateral tilt or completely lateral position at all times after entering the labor room except when placed in the sitting position for 15 minutes at the time of the first epidural injection to establish perineal analgesia. The resultant lack of aortocaval compression by the gravid uterus may further explain the absence of marked blood pressure decreases in our patients.

The one patient who required a vasopressor because of a 33 per cent drop in mean arterial blood pressure responded readily to intravenous ephedrine and did not prove hyperreactive to this agent. Ephedrine does not compromise and usually improves uterine blood flow in the presence of maternal hypotension secondary to conduction anesthesia.[8] It was given in 7.5 mg. increments in case the patient proved to overrespond to a vasopressor agent as is reputed to occur in pre-eclampsia.

The rise in blood pressure and pulse, in spite of good analgesia, as the patients neared the second stage, could be explained by anxiety in anticipation of delivery. Patients were allowed to push up to 30 minutes after reaching second stage and this increased muscular activity would also tend to increase blood pressure and pulse. The inability of epidural analgesia to sensory levels of the sixth to the eighth thoracic vertebra to control blood pressure in several of our gestational hypertension subjects at moments of increased mental stimulation or anxiety underscores the fact that this form of analgesia cannot serve as the sole method of treatment during labor and delivery in severe pre-eclampsia. Additional measures must be considered if hyperactivity, increased hypertension, and possibly seizures are to be prevented.

In normal pregnancy a substantial increase occurs in glomerular filturation rate (GFR) and renal plasma flow (RPF). As a result blood urea nitrogen (BUN) and creatinine levels are lowered to 6 to 8 and 0.4 to 0.6 mg. per 100 ml., respectively.[6] The levels of BUN (mean 18.2) and creatinine (mean 0.75 mg.) in our patients, though normal for nonpregnant patients, are high for normal pregnancy and probably represent decreased renal function. Pre-eclampsia is characterized by reduced GFR, RPF, plasma volume, and aldosterone secretion.[4] In normal patients during labor renal activity increases and polyuria is frequent despite a 25 per cent reduction in GFR and RPF.[5] This reduction might be explained by aortocaval compression in the supine position. All of our patients labored in the lateral tilt position. Epidural block to the level of the eighth thoracic vertebra will denervate the kidneys and adrenals.[7] Bonica[5] stated that specific sympathetic block effectively relieves renal arterial spasm, thereby increasing RBF and urinary output. Acute renal denervation in dogs is followed by a rapid and impressive increase in urinary sodium concentration and excre-

tion independent of changes in renal hemodynamics.[9] Because pre-eclampsia is associated with generalized vasoconstriction and because epidural analgesia to the level of the eighth thoracic vertebra should decrease renal arterial spasm we examined the effect of this form of analgesia on GFR and urinary output in pre-eclamptic patients. Although not as ideal as inulin clearance, creatinine clearance and sodium excretion may be used as an index of glomerular filtration; we selected these techniques to avoid the injection of a foreign substance into a pregnant patient.[10] Although renal tubular reabsorption plays more of a role in sodium excretion the latter is also influenced by GFR[10] and was used as a further method of evaluating changes in GFR. We were unable to demonstrate either significant increases in GFR or urinary output; however, renal function was not adversely affected by epidural analgesia. The slight increase in creatinine clearance and sodium excretion during the first hour after initiation of epidural analgesia might be explained by acute renal denervation and subsequent renal vascular vasodilation and increased blood flow. However, the 15 minute period of sitting upright after the first epidural injection might also have influenced the first hour postepidural values by altering the relationship of the pregnant uterus to the aorta, vena cava, renal vessels, and ureters. The explanation for the lack of improved renal function may be found in the renal lesion of pre-eclampsia. This does not consist solely of vasoconstriction, for the glomerular capillary endothelium is swollen and fibrinoid material is deposited between the swollen cells along the basement membrane.[3] The resultant narrowing of capillary lumina is sufficient explanation for the reduced GFR.[4] Furthermore, although the degree of constriction of the afferent and efferent glomerular arterioles is at least partially under neural control both vessels possess an inherent degree of tonic contraction which is independent of neural influence,[10] and thus may not be affected by sympathetic block. The mild mean arterial blood pressure fall in our patients should not have influenced GFR or urinary output since in the presence of systemic arterial hypotension dilation of the afferent arteriole with constant efferent arteriolar resistance maintains glomerular hydrostatic pressure and GFR until mean arterial pressure falls below 70 or 80 mm. Hg. Meperidine and morphine cause a significant reduction in GFR and ERPF with a diminished urine flow. These effects in the absence of significant falls in systemic blood pressure have been interpreted as evidence of intrarenal vasoconstriction.[11] We were able to avoid this problem since narcotics were not necessary for our patients.

Progressive maternal acidosis may occur in labor managed without epidural analgesia.[12] This would be an added stress to patients who are already compromised by gestational hypertension or pre-eclampsia. The maintenance of a stable acid-base state in our patients is probably due to the absence of painful labor preventing increased maternal somatic muscle activity. We also attempted to maintain maternal hydration by administration of intravenous dextrose and water at the moderate rate of 70 to 80 ml. per hour. Hyperventilation in response to painful contractions may contribute to maternal dehydration and was avoided by employing epidural analgesia.

The good Apgar scores and normal umbilical blood gases and acid-base balance indicate a lack of infant depression. Infant benefits are derived from avoiding depressant narcotics and by decreasing trauma by means of good perineal relaxation and controlled delivery under epidural analgesia.

In summary, although unable to show improved renal function in patients with gestational hypertension during epidural analgesia for labor and delivery, we also failed to note significant deterioration of renal function. Maternal blood pressure was controlled safely by epidural analgesia and, although mental stimulation or anxiety caused impressive transient increases in blood pressure, similar changes due to painful labor were avoided. The maintenance of normal maternal oxygenation and acid-base status plus the absence of newborn depression are added benefits of epidural analgesia. This form of therapy is recommended as valuable and safe in patients with gestational hypertension. Whether or not this can be extended to patients with documented pre-eclampsia remains to be determined. Because of the lack of ability to control acute increases in blood pressure secondary to emotional stimuli epidural analgesia should not be employed as the sole form of management of severe pre-eclampsia during labor and delivery.

The authors thank Drs. Dennis Blainey and J. Selwyn Crawford for their advice regarding this study. Dr. Hamid Naiem and Sister Pam Milan provided helpful technical assistance. Margaret Crawley and her biochemistry staff were most helpful in carrying out the numerous biochemical determinations.

REFERENCES

1. Crawford, J. S.: Principles and Practice of Obstetric Anaesthesia, Ed. 3, Oxford, London, Edinburgh, Melbourne, 1972, Blackwell Scientific Publications, Publishers, p. 160.

2. Moir, D. D., and Willocks, J.: Br. J. Anaesth. **40:** 129, 1968.
3. Speroff, L.: Am. J. Cardiol. **32:** 582, 1973.
4. Page, E. W.: J. Obstet. Gynaecol. Br. Commonw. **79:** 883, 1972.
5. Bonica, J. J.: Principles and Practice of Obstetric Analgesia and Anesthesia, Philadelphia, 1967, F. A. Davis Co., Publishers, P. 1135.
6. Berman, L. B.: J. A. M. A. **230:** 111, 1974.
7. Marx, G. F.: International Anesthesiology Clinics: Obstetric Complications, vol. 6, Boston, 1968, Little, Brown & Company, Publishers, p. 841.
8. James, F. M., Greiss, F. C., and Kemp, R. A.: Anesthesiology **33:** 25, 1971.
9. Sertorius, D. W., and Burlington, H.: Am. J. Physiol. **185:** 407, 1956.
10. Renkin, E. M., and Robinson, R. R.: N. Engl. J. Med. **290:** 785, 1974.
11. Loughridge, L.: Scurr, L., and Feldman, S. editors: *In* Anaesthesia, London, 1974, William Heinemann Medical Books, Ltd., Publishers, p. 319.
12. Pearson, J. F., and Davies, P.: J. Obstet. Gynaecol. Br. Commonw. **81:** 971, 1974.

Response of human uterine arteries to local anesthetics

LUIS A. CIBILS, M.D.*

Chicago, Illinois

The in vitro effects of local anesthetics and norepinephrine upon strips of early gestation and term pregnancy uterine arteries were studied in eight cases. In another case, the effect upon uterine veins was studied with a standard organ bath used to record isometric contractions. Histologic preparations were made to verify the type of vessel studied. An artery obtained from an eight-week gestation did not respond to either lidocaine or mepivacaine. All other arterial specimens (radial and helicoidal strips) responded with slow, rising, strong contractions to diluted concentrations of both of these substances. Likewise they responded with rapid contractions when exposed to norepinephrine. Alpha blockers were unable to prevent the contractions triggered by the local anesthetics. The vein specimens did not respond to local anesthetics but contracted when stimulated by norepinephrine. Based on these observations and after brief review of some hypotheses advanced to explain post–paracervical anesthesia fetal bradycardia, it is postulated that this bradycardia is probably due to uterine artery spasm, causing decreased intervillous space blood flow and fetal hypoxia.

THE HIGH INCIDENCE OF post–paracervical block fetal bradycardia is a distressing observation which has not yet been satisfactorily explained. In the thorough review of the subject, Thiery and Vromans[16] surveyed the various hypotheses advanced. They may be classified in three groups: (1) a reflex action; (2) hypoxia; and (3) a toxic effect of medication. The latter has been persistently studied by Teramo[15] and Asling and associates,[1] but some observations by others regarding fetal blood levels of anesthetic cast doubt about the validity of this hypothesis. The hypoxic mechanism has been postulated to be mediated by a number of possible steps: maternal hypotension, mechanical compression of vessels by the injected solutions, and epinephrine-triggered placental vessel constriction.[16] Murphy and colleagues,[11] and Vasicka and co-workers[17] also propose this latter mechanism, added to uterine hypercontractility. There is a great deal of controversy among the many papers published to such an extent that none of the postulated mechanisms can explain the majority of the commonly observed fetal heart rate changes.

From the University of Chicago, Chicago Lying-in Hospital.

Received for publication October 17, 1975.

Accepted December 16, 1975.

Reprint requests: Dr. Luis A. Cibils, Department of Obstetrics and Gynecology, 5841 Maryland Ave., Chicago, Illinois 60637.

**Mary Campau Ryerson Professor of Obstetrics and Gynecology.*

It is possible that other mechanisms, as yet unexplored, may be the triggering factors in the sequence of events ending in fetal bradycardia. One of them, which could well be important, is the possible stimulating effect of local anesthetics on the uterine artery walls which, in turn, would cause vasoconstriction. This idea was originally based on the observations made by Moawad and Hendricks[10] who by injecting 1 per cent procaine into puerperal myometrium produced marked local hypercontractility. The same effect, which resulted in labor, was later observed on the undelivered term pregnant uterus.[4] Of course, myometrium is not vascular smooth muscle; therefore, an extrapolation of these results is unwarranted. However, the personal observation, through the years, that infiltration of the femoral artery before insertion of a catheter was often followed by transient loss of pulsation suggested that it was worthwhile to study the effects of these drugs upon the uterine arteries.

The observations made in vitro with specimens obtained at cesarean hysterectomies are the subject of the present report.

Material and methods

Specimens from nine patients were studied. Four were obtained at hysterectomies during the first and second trimester of pregnancy (8, 12, 14, and 20 week's gestation), and five were from cesarean hysterectomies at term. The uterine vessels were identified and marked with a stitch at the time of clamping and

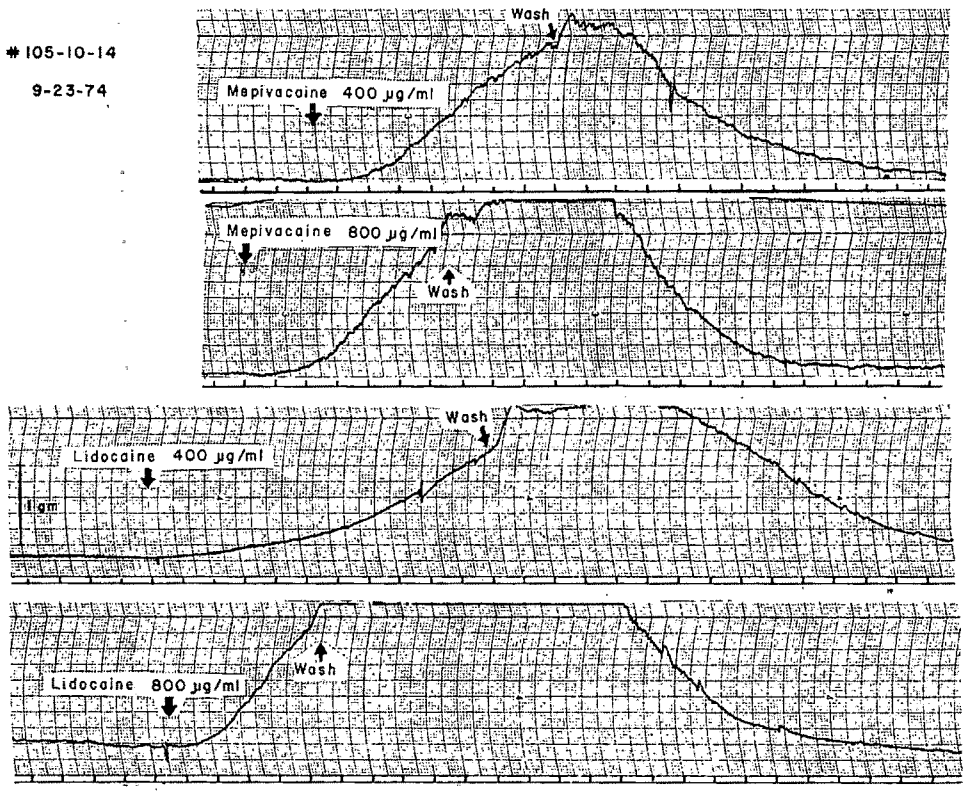


Fig. 1. In vitro response of radial uterine artery strips obtained from term pregnancy. Note the steeper rise of the contraction wave with higher drug concentrations, as well as the more prolonged time taken for relaxation. These times are longer for lidocaine. Lidocaine and mepivacaine seem equipotent regarding stimulation. In these and subsequent records, time is marked in minutes in the ordinates, and five thick lines in the abscissa represent 1 Gm. of tension. Addition of the anesthetic to the bath and its final concentration are shown by the arrow. Arrows also indicate the washing with fresh Krebs solution.

section of the pedicles. Immediately after removal of the uterus, in the operating room, the identified vessel was dissected about 5 cm. above the area crushed by the hemostatic forceps, cut, and immersed in Krebs solution to be transported to the laboratory where they were bubbled with 95 per cent oxygen and 5 per cent carbon dioxide.

The strips were suspended in a 50 ml. organ bath, submerged in a larger bath, and maintained at a constant 37° C. temperature. Stainless steel hooks were passed through the ring in radially cut specimens and through artifical perforations at each end in helicoidal strips; the lower hook was fixed to the base of the organ bath, while the top hook was connected, by means of a cotton thread, to a strain guage* for recording isometric tensions. A tension of 1 Gm. was applied to all specimens and left to stabilize for at least 45 minutes before the studies began. The observations were recorded on a four-channel polygraph apparatus* set to a sensitivity of 2 Gm. for a full range of deflection. The Krebs solution, freshly prepared, had the following composition in milliequivalents per liter: $Na+$, 141; $K+$, 5.9; $Ca++$, 5.1; $Mg++$, 2.4; $Cl-$, 104.8; H_2PO_4-, 2.2; HCO_3-, 24.9; SO_4--, 2.4; glucose, 10. Oxygenation was maintained by continuous bubbling of 95 per cent oxygen and 5 per cent carbon dioxide.

Standard solutions of local anesthetics (one per cent lidocaine hydrochloride† and mepivacaine hydrochloride‡) were added to the organ bath in volumes ranging from 0.25 to 4 ml. to make concentrations of 50 to 800 µg per milliliter. Furthermore, highly diluted solutions of norepinephrine, 0.1 to 8 µg per milliliter

*No. 350, Statham Instruments, Inc., 2230 Statham Blvd., Oxnard, California 93030.

*Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, California 92634.

†Xylocaine, Astra Pharm. Products, Inc., 7 Neponset St., Worcester, Massachusetts 01606.

‡Carbocaine, Winthrop Labs., Div. of Sterling Drug Inc., 90 Park Ave., New York, New York 10016.

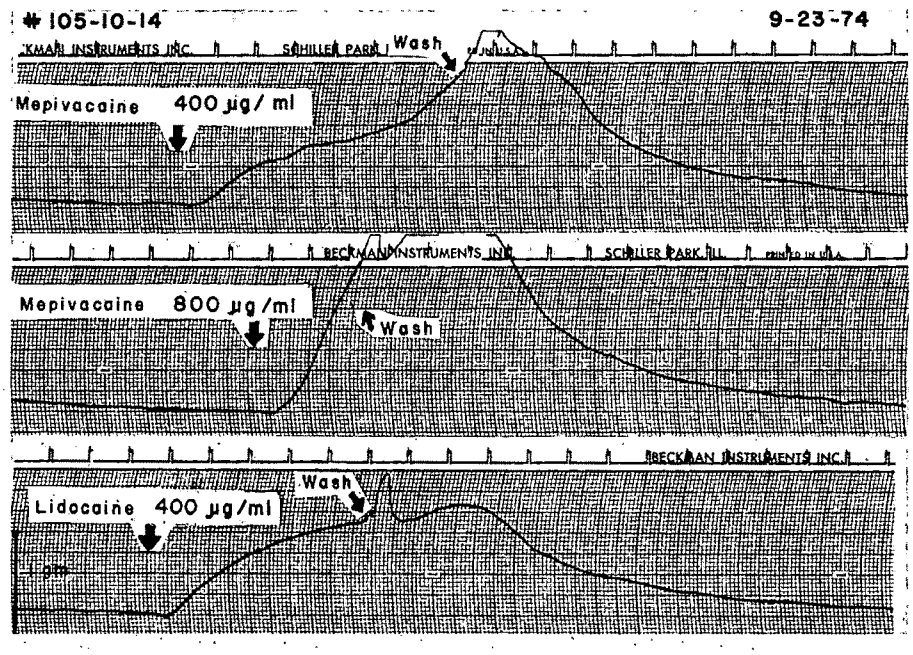


Fig. 2. Helicoidal strips taken from the same case shown in Fig. 1. The stimulations recorded are very similar to those obtained with radial strips. There is a very clear dose-response relationship.

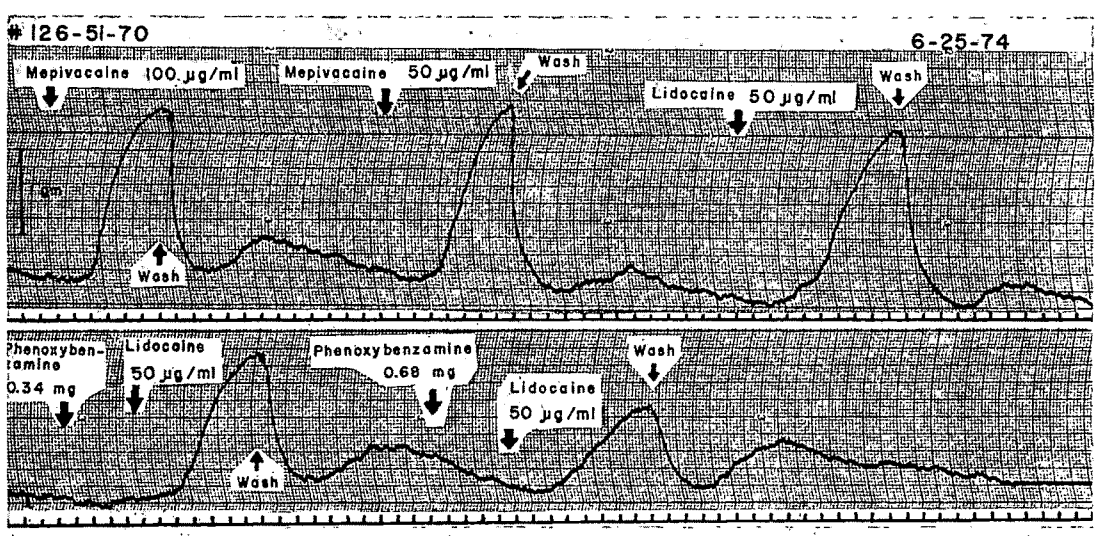


Fig. 3. Radial uterine artery strips from a term pregnancy stimulated with decreasing doses of mepivacaine and lidocaine. There is a good, almost maximal response followed by rapid, smooth relaxation after washing. In the lower tracing, the addition of 7 µg per milliliter of phenoxybenzamine did not block the stimulation produced by lidocaine. Doubling the concentration to 14 µg per milliliter diminished but did not abolish the response.

to make concentrations of 0.006 to 0.16 µg per milliliter, and the α-adrenergic–blocking agent phenoxybenzamine, 0.5 to 2 ml. to make concentrations of 7 to 14 µg per milliliter, were added in some cases.

Histologic verification. After the studies were completed, the specimens were removed from the bath and fixed in 10 per cent formalin solution for subsequent histologic preparation. The sections were stained with standard hematoxylin and eosin, Masson's trichrome,[8] and Verhoeff's elastic tissue staining[9] methods in order to ascertain the type of vessel studied.

Analysis of recordings. It was relatively simple to observe the pharmacologic effects of the substances under study because neither the radial nor the helicoi-

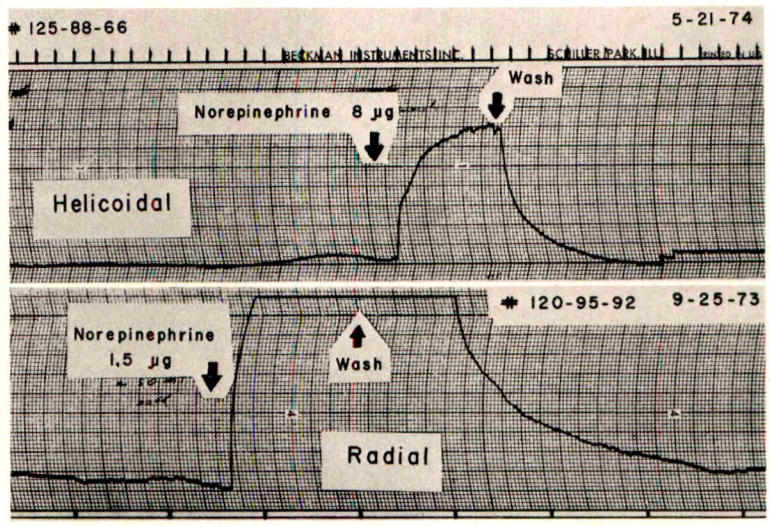


Fig. 4. Helicoidal and radial strips of term pregnancy uterine artery strips respond with strong contractions when exposed to norepinephrine concentrations of 0.16 and 0.03 μg per milliliter, respectively. Relaxation followed sometime after washing, and its duration was proportional to the drug concentration. Note that the paper speed was five times faster in the bottom tracing.

dal strips showed detectable spontaneous activity at the set tension. The time elapsed from addition of the substance to start of the contraction was noted, as well as the time to reach maximum tension within the stated range; the slope of the contraction wave was also noted.

Dose-dependent responses to stimulation by the local anesthetics were observed. The possible sympathetic-mediated mechanism was studied with an α-adrenergic–blocking agent before the strips were exposed to the anesthetic. Conversely, the stimulatory effect of norepinephrine was elicted in some preparations.

In all preterm pregnancies, only the uterine arteries were studies (four cases). Of the term cases, in four the uterine arteries were studied, and in one the uterine veins were studied.

Results

Arteries.

Term pregnancy. The exposure of radial or helicoidal strips from term pregnancies to 400 to 800 μg milliliter of either one of the two local anesthetics studied is illustrated in Figs. 1 and 2. There is a distinct delay period before the slow rising contraction increases the tension on the strip; this may range from 15 to 180 seconds, depending upon the case and the concentration of the anesthetic. On the other hand, the steepness of the rising contraction is dose-dependent; therefore, the time to reach maximum tension (or go off the recording scale) ranges between 500 and 80 seconds (Table I and Figs. 1, 2, and 3). None of the specimens tested failed to respond to the medications used at the concentrations mentioned. In almost all specimens, there was a rebound contraction immediately after washing of the strip, and this was followed by a slow relaxation which took up to 20 minutes to regain the base-line tension. Very characteristically, the duration of this relaxation period was in direct proportion to the concentration of the anesthetic solution (compare Fig. 3 with Figs. 1 and 2).

Table I. Cases of term pregnancy: Ranges of time elapsed (in seconds) between exposure of the specimens to the anesthetics and start of the response and the same from beginning to maximum response

	Lidocaine		*Carbocaine*	
Case	*Time to start*	*Time to maximum*	*Time to start*	*Time to maximum*
1	15-30	40-160	80-180	150-500
2	120-180	150-360	180-300	420-500
3	60	220	120	120-240
4			80-210	360-500

The exposure to extremely low concentrations of norepinephrine triggered significant responses (Fig. 4); therefore, it was decided to investigate whether this neurohormone or its receptors were involved in the mechanism of stimulation by the local anesthetics. The prior exposure to significant concentrations of an α-blocking agent did diminish somewhat the contractile response but was far from blocking it (Fig. 3), even at very high concentrations.

The histologic sections of the specimens used in these observations are shown in Figs. 5 and 6.

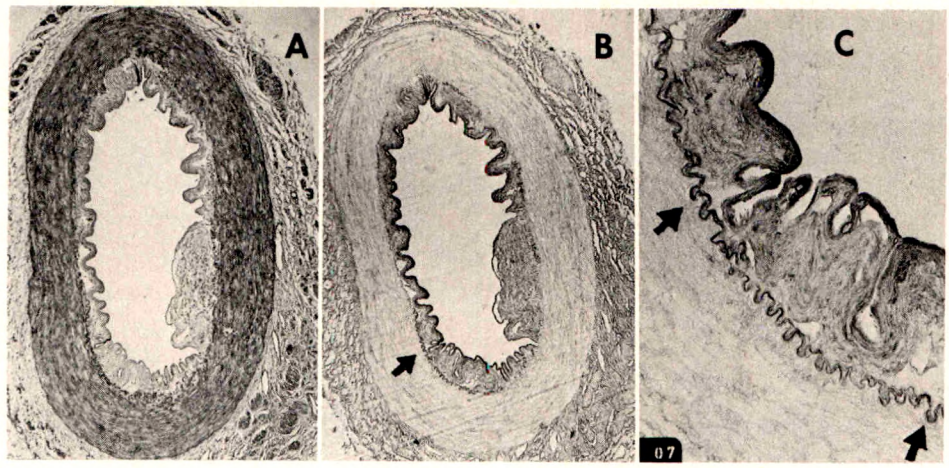


Fig. 5. No. 105-10-14. Histologic sections made from specimen studied in Fig. 1. *A,* Masson trichrome stain shows the rich, thick muscular circular layer and the adventitia. (Original magnification ×50.) *B,* Verhoeff elastic stain illustrates the thin waving subendothelial elastic layer better seen at the arrow. (Original magnification ×50.) *C,* High magnification of this field to better illustrate the elastic layer and folded endothelium. (Original magnification ×250.)

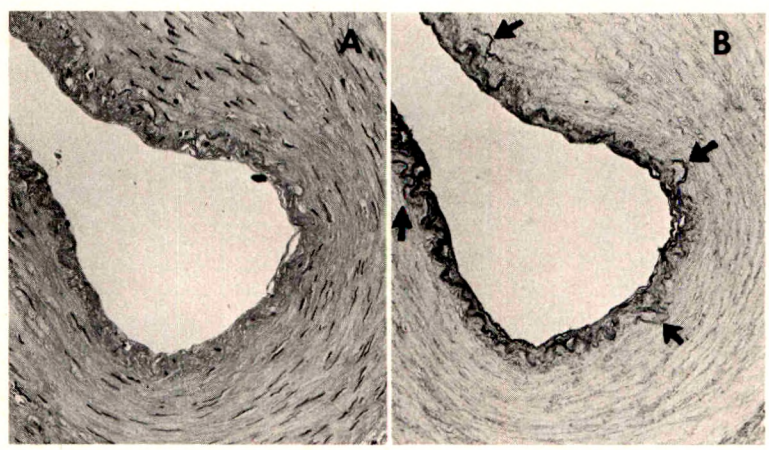


Fig. 6. No. 126-51-70. Specimen used in observation shown in Fig. 3. *A,* Hematoxylin-eosin staining shows the circular muscular layer and smooth endothelium. (Original magnification ×250.) *B,* Verhoeff eleastic stain shows interrupted elastic layer (arrows) under the unfolded endothelium. (Original magnification ×250.)

Early pregnancy. Specimens from early gestations were exposed to the same concentrations of the local anesthetics, and it was found that their responses varied (Table II). First-trimester artery specimens did not have altered tension, while second-trimester specimens responded in much the same way as those taken from term uteri. They, too, responded faster, with steeper contractions and a longer relaxation period, as the drug concentration increased in the organ bath (Fig. 7). The histologic section of the specimen used for illustration is shown in Fig. 8.

Veins. Even though the uterine veins have a very good muscular wall (Fig. 9), neither helicoidal nor radial strip specimens responded to exposure to rather high concentrations of the local anesthetics (Fig. 10). Exposure to norepinephrine was successful in producing mild contractions which started very soon.

Comment

It may be surprising that radial and helicoidal strips of uterine arteries do not show spontaneous fluctuating activity in the preparation reported here. However, the same observation was made by Cutchin and associates[5] who reported recurrent spontaneous contraction only

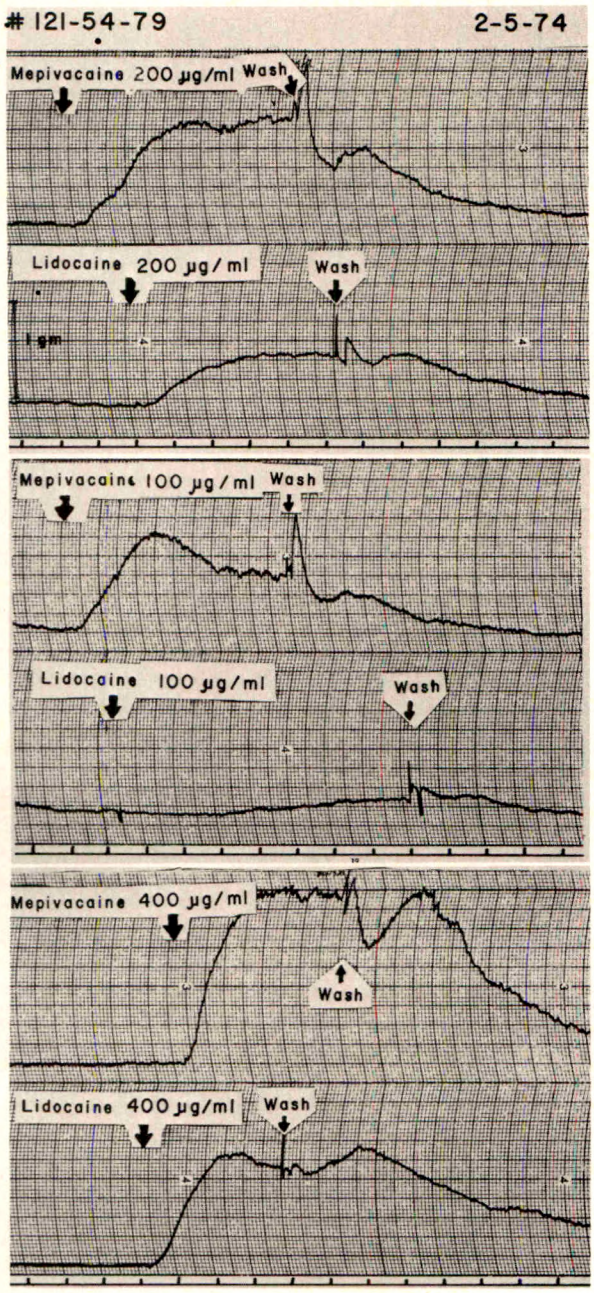


Fig. 7. Increasing dose-response relationship to both drugs studied with radial uterine artery strips of early second trimester (14 weeks) specimen. Note the slight and consistently different response to lidocaine and mepivacaine. Furthermore, the higher the concentration, the longer the relaxation period to reach control levels.

with tubular specimens in a similar type of preparation. At 1 Gm. of tension they appeared to be very stable.

The present observations indicate that lidocaine and mepivacaine are potent vasoactive drugs when applied to pregnant uterine arteries. These findings may have

Table II. Cases of early gestation: Ranges of time elapsed (in seconds) between exposure of the specimens to the anesthetics and start of the response and the same from beginning to maximum response

	Lidocaine		*Carbocaine*	
Weeks of gestation	*Time to start*	*Time to maximum*	*Time to start*	*Time to maximum*
8				
12	90-160	90-500	50	210
14	10-30	120-180	20	120
20	60-120	100-300	90	240

interesting clinical implications because it is well known that in a considerable percentage of cases in which paracervical block analgesia is used transient episodes of marked fetal bradycardia occur,[11, 15–17] the mechanism of which is still unclear.[1, 15, 16]

Studies on rabbit aortas with the use of lidocaine concentrations comparable to the lowest ones used in the present study indicate that lidocaine potentiates the stimulatory effect of epinephrine.[3, 14] However, mepivacaine seems to be an antagonistic to this stimulatory effect at all concentrations studied,[3] and lidocaine becomes antagonistic when larger doses were used (900 μ per milliliter). These two drugs strongly stimulate human uterine artery specimens from advanced gestations, as shown in the present study.

Helical human uterine artery strips are strongly stimulated by norepinephrine,[5] an observation substantiated by the present report. On the other hand, pregnant human uterine smooth muscle is also easily stimulated by procaine either in vitro[7] or in vivo,[4, 10] which is the same effect produced by lidocaine.[7] In advanced pregnancy the response of human uterine arteries appears similar to that of the myometrium, whereas in very early gestation these responses seem refractory to stimulation by the local anesthetics. One may reasonably ask: Do pregnancy changes, as they progress, increase the sensitivity of these vessels to certain agents? What is the mechanism mediating this pharmacologic action? At this time it is impossible to answer the first question, but one may say, in partial answer to the second question, that it is not through the adrenergic receptors because an α-blocker cannot prevent the local anesthetic–induced contraction. On the other hand, uterine veins with a thick muscular layer respond to norepinephrine but seem refractory to stimulation by local anesthetics. From this it is reasonable to conclude that the muscular layers of pregnant uterine arteries and veins have different pharmacologic responses to these substances.

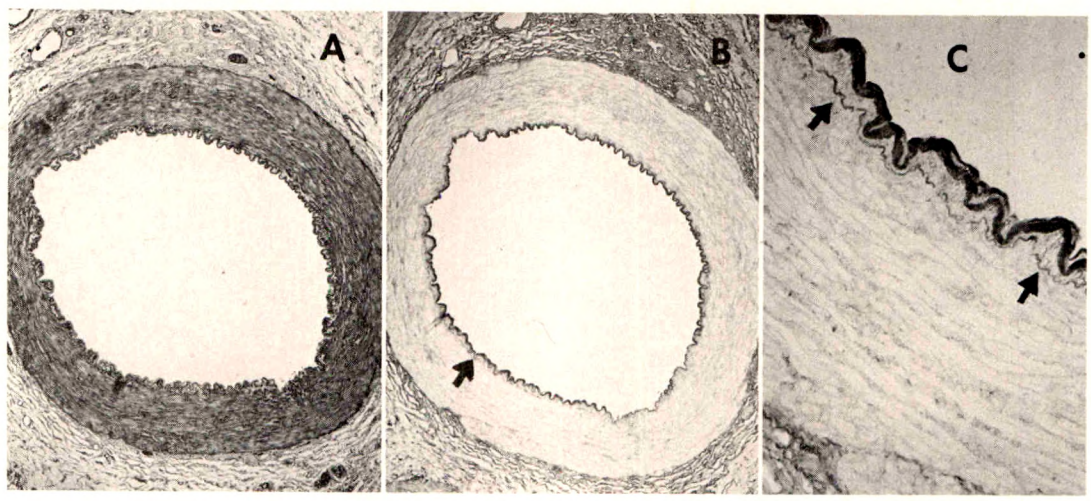


Fig. 8. No. 121-54-79. Histologic sections of specimens used in observations shown in Fig. 7. *A*, Masson trichrome stain illustrates the compact muscular circular layer and the rich adventitia. (Original magnification ×50.) *B*, Verhoeff elastic stain shows wavy subendothelial elastic layer. (Original magnification ×50.) The area shown by the arrow is magnified in *C* to illustrate more clearly the elastic layer pointed to by the arrows. (Original magnification ×250.)

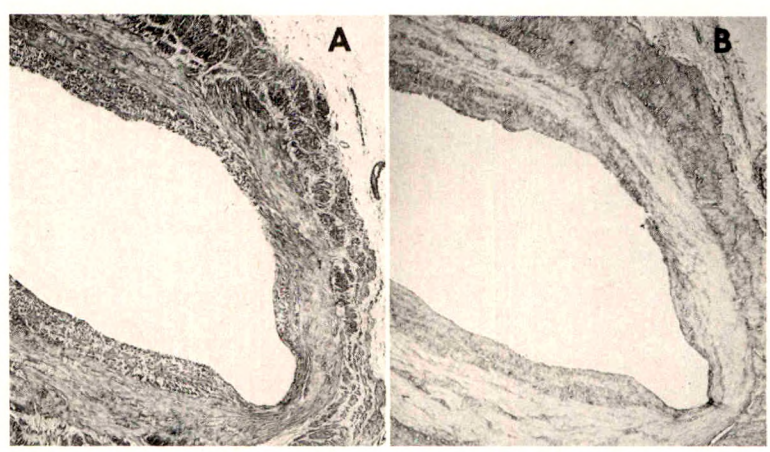


Fig. 9. No. 109-68-41. Histologic sections obtained from radial strips from term pregnancy uterine veins. *A*, Masson trichrome stain shows two distinct muscular layers: internal thin circular and external longitudinal. (Original magnification ×50.) *B*, Verhoeff elastic stain of next section reveals absence of elastic tissue or layer; the endothelium is very smooth and unfolded. (Original magnification ×50.)

Koback and colleagues[6] have shown that substances injected in the paracervical spaces tend to diffuse along the areas of least resistance, among which reasonably could be the tissues surrounding the pedicles of the uterine vessels. The observations reported here indicate that the uterine arteries respond with a sustained contraction when exposed to concentrations of these anesthetics 15 to 50 times lower than those usually found in standard preparations for local administration. Therefore, it is conceivable that a strong uterine artery spasm may follow the administration of a paracervical block if the drug diffuses close to the artery. The intensity and duration of the spasm should be proportional to the concentration of the drug and its clearance rate from the area.

A logical corollary of such a spasm—of more or less long duration—will be decreased blood flow through the spastic uterine arteries and, consequently, decreased oxygen supply to the intervillous space. It has been shown that the primate fetus responds to acute

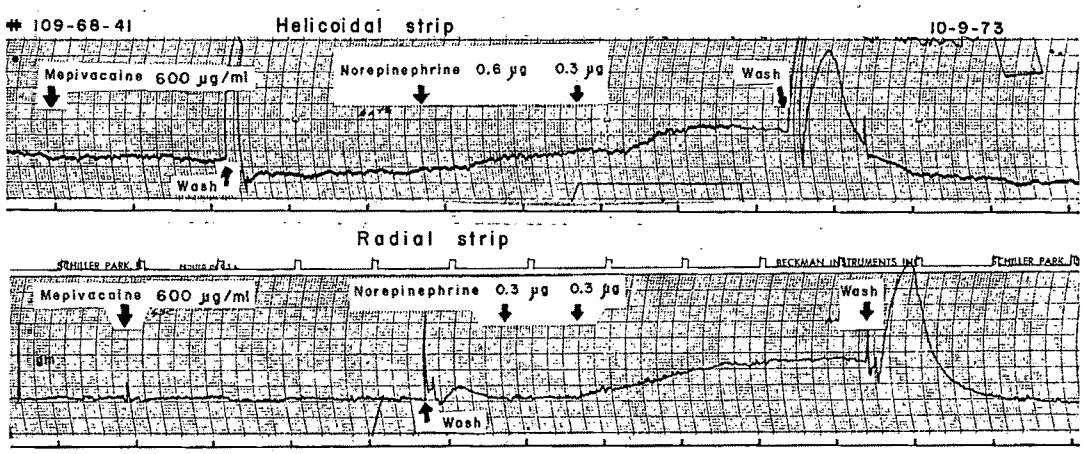


Fig. 10. In vitro response of helicoidal (top) and radial (bottom) strips obtained from term pregnancy uterine veins. Neither one responded to high concentrations of mepivacaine. Both strips responded quickly but mildly to stimulation with 0.018 and 0.012 μg per milliliter of norepinephrine.

hypoxia with bradycardia and that this bradycardia can be triggered by diminishing lower abdominal aortic blood pressure.[13] The speed with which this bradycardia begins is dependent upon pre-existing fetal oxygen content. Likewise, the lamb fetus responds with significant bradycardia when the oxygen supply of the intervillous space is decreased as a consequence of diminished uterine blood flow.[2] The lamb and primate fetuses seem to respond in a similar fashion to this type of stress. The lamb fetus in acute experiments withstands up to 50 per cent diminution of uterine blood flow without cardiovascular manifestations of distress.[2] It is not known whether the healthy primate fetus has the same high threshold. However, it is known that the unstressed fetus takes a longer time than the partially stressed one to develop bradycardia when subjected to suppression of abdominal aorta blood flow.[13] Furthermore, the primate fetus may have a bradycardia threshold comparable to that of the lamb because Myers[12] reported that decreasing the maternal aortic mean pressure down to 60 or 50 mm. Hg, even for prolonged periods of time, has no effect on fetal homeostasis or heart rate, but lesser mean pressures produce rapid distress. It is reasonable to assume that such a diminished aortic pressure will bring about a significant drop in the uterine blood flow, in proportion to the fall in mean pressure. If this is the case, the primate fetus may be similar to the lamb, and the 50 mm. Hg mean aortic pressure may correspond to a decreased blood flow of approximately 50 per cent.

If the human fetus has approximately the same reserve (or high threshold) as those of the two species studied in the laboratory, it may well be that a uterine artery spasm produced by local anesthetics triggers a drop in the uterine blood flow. But only those in whom the spasm is very marked would have sufficent diminished blood flow to cause fetal hypoxia and bradycardia. The wide range of fetal reserve as well as the variations in the degree and duration of the spasm would explain that on the average only 20 per cent of fetuses present with bradycardia following paracervical block.[1, 15, 16, 17]

From the foregoing one may conclude that:

1. Human uterine arteries in vitro respond with strong contractions when exposed to lidocaine, mepivacaine, and norepinephrine.

2. Uterine veins do not have a changed contraction pattern when exposed to the same local anesthetics but contract when exposed to norepinephrine.

3. The mechanism whereby these anesthetic substances stimulate arterial contraction is not via the adrenergic receptors.

4. Higher concentrations of in vivo administration of paracervical block anesthesia may trigger uterine artery spasm of variable magnitude and duration.

5. It is postulated that the mechanism by which fetal bradycardia occurs after paracervical block is primarily through the following sequence of events: uterine artery spasm, diminished intervillous space blood flow, and acute fetal hypoxia.

A clinical study is being conducted in order to test the validity of this hypothesis.

I wish to express my thanks to Dr. Atef H. Moawad for allowing the use of his laboratory and to Dr. Iracema Baccarini, from the Section of Pathology, for doing the histologic studies.

REFERENCES

1. Asling, J. H., Shnider, S. M., Margolis, A. J., Wilkinson, G. L., and Way, E. L.: Paracervical block anesthesia in obstetrics, II. Am. J. Obstet. Gynecol. **107:** 626, 1970.
2. Assali, N. S., Holm, L. W., and Sehgal, N: Hemodynamic changes in fetal lamb in-utero in response to asphyxia, hypoxia, and hypercapnia, Circulation Res. **11:** 423, 1962.
3. Astrom, A.: Influence of some local anesthetics upon the adrenaline contraction of isolated strips of rabbit aorta, Acta Physiol. Scand. **60:** 30, 1964.
4. Belitzky, R., Delard, L. G., and Novick, L. M.: Oxytocic effect of intramyometrial injection of procaine in a pregnant woman, Am. J. Obstet. Gynecol. **107:** 973, 1970.
5. Cutchin, J. H., McGaughey, H. S., Scoggin, W. A., Harbert, G. M., and Thorton, W. N.: Contractility of the isolated human uterine artery, Am. J. Obstet. Gynecol **90:** 143, 1964.
6. Koback, A. J., Sadove, M. S., and Mazeros, W. T.: Anatomic studies of transvaginal regional anesthesia, Obstet. Gynecol. **19:** 302, 1962.
7. McGaughey, H. S., Corey, E. L., Eastwood, D., and Thornton, W. N.: Effect of synthetic anesthetics on the spontaneous motility of human uterine muscle in-vitro, Obstet. Gynecol. **19:** 233, 1962.
8. McManus, J. F., and Mowry, R. W.: Staining Methods. Histological and histochemical, Paul B. Hoeber, Inc., Medical Book Division of Harper & Row, Publishers, New York, 1960, p. 61.
9. McManus, J. F., and Mowry, R. W.: Staining Methods. Histological and histochemical, Paul B. Hoeber, Inc., Medical Book Division of Harper & Row, Publishers, New York, 1960, p. 240.
10. Moawad, A. H., and Hendricks, C. H.: Spontaneous and pharmacologically induced disruption of myometrial activity in the early puerperium, Am. J. Obstet. Gynecol. **98:** 1091, 1967.
11. Murphy, P. J., Wright, J. D., and Fitzgerald, T. B.: Assessment of paracervical nerve block anesthesia during labour, Br. Med. J. **1:** 526, 1970.
12. Myers, R. E. Two patterns of perinatal brain damage and their conditions of occurrence, Am. J. Obstet. Gynecol. **112:** 246, 1972.
13. Myers, R. E., Mueller-Heubach, E., and Adamsons, K.: Predictability of the state of fetal oxygenation from a quantitative analysis of the components of late decelerations, Am. J. Obstet. Gynecol. **115:** 1083, 1973.
14. Nava-Rivera, A., Gutierrez-Lopez, A., Ferez, A., and Eisenberg, J.: Influence of procaine, lidocaine and prilocaine on the adrenaline contraction of isolated strips of rabbit aorta, Arch. Int. Pharmacodyn. **169:** 308, 1967.
15. Teramo, K.: Effects of obstetrical paracervical blockade on the fetus, Acta Obstet. Gynecol. Scand. **50:** 6, 1971. (Suppl 16.)
16. Thiery, M., and Vromans, S.: Paracervical block analgesia during labor, Am. J. Obstet. Gynecol. **113:** 988, 1972.
17. Vasicka, A., Robertazzi, R., Raji, M., Scheffs, J., Kosmowski, J., and Goei, T.: Fetal bradycardia after paracervical block, Obstet. Gynecol. **38:** 500, 1971.

Placental function and renal tract studies in pre-eclampsia with proteinuria and long-term maternal consequences

JOHN R. H. FLIEGNER, M.D.

Melbourne, Victoria, Australia

A total of 99 patients with pre-eclampsia and proteinuria were managed conservatively between 30 and 37 weeks of gestation, based on serial urinary estriol, liquor amnii, and renal function studies. The over-all perinatal wastage was 14 per cent, but was 35 per cent in association with subnormal estriol excretion and oligohydramnios (<250 ml.). In severe pre-eclampsia (blood pressure >170/110 mm. Hg with proteinuria >5 Gm. per liter) the incidence of subnormal estriol was 73 per cent and, because of this and the associated maternal hazards, conservative treatment had little place. However, in less severe pre-eclampsia with proteinuria early in the third trimester, this prospective study, based on serial placental and renal function tests, showed that frequently the pregnancy could be prolonged and fetal losses due to prematurity avoided. It should be stressed that such conservative treatment should not be continued when there are strong clinical contraindications. Irrespective of the severity of the prior pre-eclampsia, it was unusual for patients to show residual hypertension, proteinuria, or abnormal pyelography at their postnatal examination. Postpartum renal biopsy showed either normal histology or regression of the classical glomerular lesion in 77 per cent of cases.

IN CONSIDERING the maternal and fetal consequences of pre-eclampsia in the third trimester of pregnancy, and particularly the degree of placental dysfunction, some grading of the condition is necessary. Previous reports agree that in general any classification which, on grounds of the degree of hypertension and proteinuria, distinguishes between mild to moderate and severe forms of pre-eclampsia, not only grades the maternal hazards, but will also roughly delimit two orders of estriol excretion and corresponding fetal jeopardy.[1–3]

Beyond 37 weeks of gestation, proteinuria exceeding 1 Gm. per liter in association with hypertension usually warrants delivery on clinical grounds alone. However, between 30 and 37 weeks of gestation, the timing of delivery is difficult and often with uncertain results. Traditional teaching advocates termination of the pregnancy by amniotomy if after conservative treatment for 24 hours there is persistent proteinuria and hypertension. Fetal losses due to gross prematurity are accepted as inevitable. In 1968, Reid and co-workers[3] suggested that in patients with mild and moderate pre-eclampsia in association with normal estriol excretion, induction of labor should not be performed before 37 weeks of gestation for fetal indications alone. Booth and co-workers[4] and Müller and Nielson[5] took the opposite view. In terms of clinical application they were not enthusiastic about the value of estriol assays in patients with pre-eclampsia.

The current prospective study was undertaken to assess the following: (1) the value of serial urinary estriol assays, renal function tests, and amniocentesis in predicting fetal jeopardy in patients with pre-eclampsia and albuminuria between 30 and 37 weeks of gestation; (2) the incidence of hitherto unsuspected renal disease in patients with pre-eclampsia after 30 weeks of gestation; (3) the degree of reversibility of the renal lesion and impairment of renal function in pre-eclampsia; and (4) long-term consequences of pre-eclampsia with an evaluation of the likelihood of residual hypertension or renal damage if a more conservative treatment of pre-eclampsia is adopted.

Material and methods

Patients were considered to have severe pre-eclampsia if the blood pressure at any stage exceeded

From the Department of Obstetrics and Gynaecology, University of Melbourne and Royal Women's Hospital.

Received for publication September 25, 1975.

Accepted January 20, 1976.

Reprint requests: Dr. J. Fliegner, University of Melbourne, Dept. of Obstetrics and Gynaecology, Parkville, Victoria 3052 Australia.

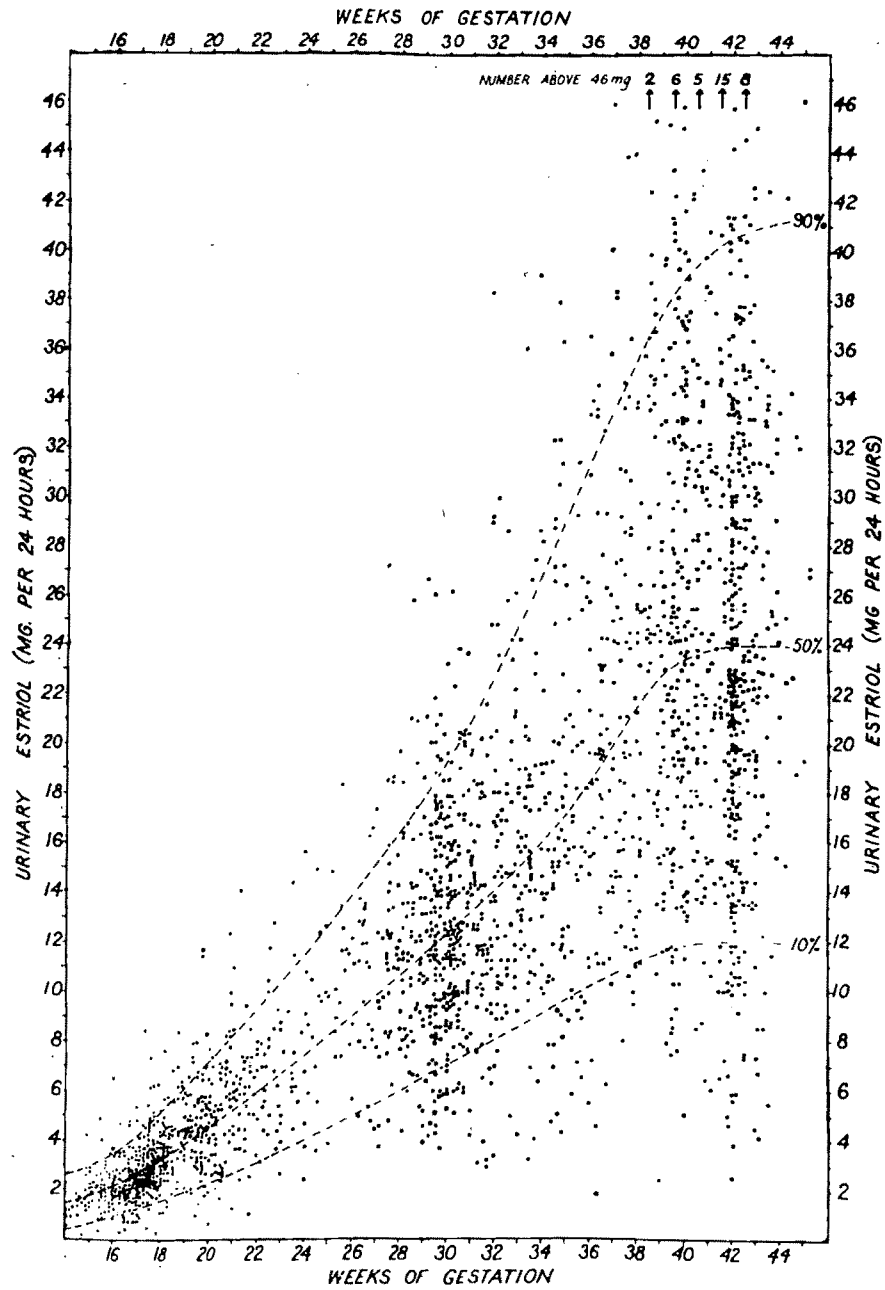


Fig. 1. Estriol values in a normal obstetric population. The tenth, fiftieth, and ninetieth percentile lines are shown.

170/110 mm. Hg in association with proteinuria of greater than 5 Gm. per liter. Moderately severe preeclampsia was deemed to exist in those cases with a blood pressure above 140/90 mm. Hg but less than 170/110 mm. Hg in association with proteinuria exceeding 1 Gm per liter. Patients with known underlying chronic renal disease were excluded from the study, as were those with multiple pregnancy, diabetes mellitus, and erythroblastosis. Similarly, those patients in whom there was cessation of the fetal heartbeat at the time of admission to hospital were not considered. Parenteral sedation, anticonvulsants, magnesium sulfate, hypotensives, and diuretics were administered according to the clinical situation, and the following investigations were performed. (1) Twenty-four hour urinary estriol measurement was done according to the method of Brown and co-workers.[6] The completeness of the collection was checked by creatinine and/or specific gravity measurements. A subnormal estriol collection during the third trimester of pregnancy was

considered to be below the line joining 2 mg. at 20 weeks of gestation, 8 mg. at 30 weeks, 10 mg. at 35 weeks, and 12 mg. at 40 weeks of gestation (Fig. 1). Values above this line were considered to be normal. (2) Renal function was assessed with serial blood urea, uric acid, serum creatinine, and creatinine clearance determinations. (3) Amniocentesis was carried out. The nature of the liquor amnii was noted, and its volume measured by means of the dye dilution technique with sodium aminohippurate as described by Charles and Jacoby.[7] Fetal maturity was assessed by determination of the lecithin-sphingomyelin ratio (L/S ratio).

After admission to hospital and the initial assessment, all patients were tracked with thrice-weekly urinary estriol assays, renal function tests at least weekly, and amniocentesis.

The indications for termination of the pregnancy in the survey were: (1) an uncontrollable blood pressure despite hypotensive therapy, serious deterioration of renal function with a rising blood urea, or the occurrence of eclampsia; (2) the presence of meconium in the liquor at amniocentesis; (3) subnormal estriol excretion in association with meconium staining of the liquor amnii; and (4) a gestation of 37 weeks or an L/S ratio of greater than 2:1.

A critically low estriol by itself was not an indication for termination, but only if confirmed by another test and associated with meconium-stained liquor or severe oligohydramnios. The condition of the infant at birth was assessed by the Apgar score 2 minutes after delivery. Fetal growth retardation was diagnosed when the infant's birth weight was below the tenth percentile for the period of gestation as seen in patients in this community.[8]

Postpartum assessment of the mother 6 to 8 weeks after confinement included a clinical appraisal, intravenous pyelography, and renal biopsy.

Results

A total of 99 patients were considered in the study, 41 with severe pre-eclampsia and 58 with pre-eclampsia of moderate severity according to the previous classification.

Severe pre-eclampsia. The results are summarized in Tables I, II, and III. Of the 41 patients in this category, 28 were primigravidas and 13 were multigravidas. In five cases it was necessary to terminate the trial for maternal reasons-namely, an uncontrollable blood pressure (3), eclampsia (1), and deteriorating renal function (1). Fifteen patients were delivered within 1 week of admission to hospital (36.5 per cent) and there were six perinatal deaths in this category.

Table I. Duration of conservative treatment and perinatal wastage in 41 patients with severe pre-eclampsia between 30 and 37 weeks of gestation (BP > 170/110 and proteinuria > 5 Gm. per liter)

Time of delivery after admission to hospital	*No. of patients*	*Perinatal deaths*	
		*SB**	*NND*
<72 hr.	7	3	
72 hr.-1 wk.	8	2	1
1-2 wk.	14	2	
2-3 wk.	9	1	
>3 wk.	3		
Total	41	9 (22%)	

*SB = stillbirths; NND = neonatal deaths.

Table II. Indications for delivery in 41 patients with severe pre-eclampsia

Indication for delivery	*No. of patients*
Uncontrollable blood pressure, eclampsia, or deterioration of renal function	5
Critical estriol excretion	13
Intrauterine death	6
Spontaneous labor	9
Gestation of 37 wk.	8

Table III. Relationship between blood urea, estriol excretion, and perinatal outcome in 41 patients with severe pre-eclampsia

Blood urea (mg./100 ml.)	*No. of patients*	*Estriol excretion (mg./24 hr.)*		*Perinatal wastage*
		Low	*Normal*	
<40	24	17 (3)*	7	3
40-49	8	5 (1)	3	1
50-59	5	4 (2)	1	2
60-69	3	3 (2)	0	2
>70	1	1 (1)	0	1
Total	41	30 (9)	11	9

*Figures in parentheses are perinatal deaths.

Twenty-six patients were delivered more than 1 week after admission and there were three perinatal deaths in this group. Abruptio placentae occurred in two patients with severe pre-eclampsia, but in both cases the fetus survived, although premature labor occurred.

The relationship between estriol excretion, blood urea, and perinatal death in the 41 patients with severe pre-eclampsia is shown in Table III. There were no perinatal deaths in 11 patients with normal estriol values, but nine perinatal deaths occurred in 30 patients with subnormal estriol excretion. The over-all

Table IV. Duration of conservative treatment and perinatal wastage in 58 patients admitted with pre-eclampsia of moderate severity (BP < 170/110 and proteinuria > 1 Gm. per liter)

Time of delivery after admission to hospital (wk)	*No. of patients*	*Perinatal*	
		SB	*NND*
<1	6	—	—
1-2	13	1	—
2-3	17	1	—
3-4	14	1	1
>4	8	1	—
Total	58	5 (8.6%)	

Table V. Indication for delivery in 58 patients with moderately severe pre-eclampsia

Indication for delivery	*No. of patients*
Uncontrollable blood pressure or deterioration of renal function	2
Critical estriol excretion	20
Intrauterine death	1
Spontaneous labor	16
Gestation of 37 wk.	19

Table VI. Relationship between blood urea, estriol excretion, and perinatal outcome in 58 patients with pre-eclampsia of moderate severity

Blood urea (mg./100 ml.)	*No. of patients*	*Estriol excretion (mg./24 hr.)*		*Perinatal wastage*
		Low	*Normal*	
<40	50	19 (3)*	31 (1)	4
≥40	8	3 (1)	5	1
Total	58	22 (4)	36 (1)	5

*Figures in parentheses are perinatal deaths.

incidence of subnormal estriol excretion was 73 per cent. Low estriol values were present in 17 of the 24 patients with a blood urea below 40 mg. per 100 ml., and there were three perinatal deaths in this group. In 17 patients with a blood urea above 40 mg. per 100 ml., low estriol values were present in 13, and six perinatal deaths occurred in association with subnormal estriol excretion.

The over-all perinatal wastage was 22 per cent, but was 30 per cent in association with low estriol excretion. The average gestation at delivery was 35 weeks, the average birth weight 1,800 Gm. and the average placental weight 360 Gm. Pregnancy was terminated because of subnormal estriol excretion in 13 patients (31 per cent), but in another nine cases (22 per cent) the occurrence of spontaneous premature labor avoided the necessity of a decision being made as to the timing of delivery (Table II).

Table VII. Relationship between liquor volume, estriol excretion, and fetal outcome in 99 patients with pre-eclampsia and proteinuria >1 Gm. per liter

Liquor volume (ml.)	*No. of patients*	*Estriol excretion (mg./24 hr.)*		*Perinatal wastage*	*Fetal weight <10th percentile*
		Normal	*Low*		
0-250	25	4	21 (7)*	7	16
251-500	34	15	19 (6)	6	14
>500	40	28 (1)	12	1	9
Total	99	47 (1)	52 (13)	14	39

*Figures in parentheses are perinatal deaths.

Table VIII. Relationship between nature of liquor amnii, estriol excretion, and fetal outcome

Urinary estriol (mg./24 hr.)	*No. of patients*	*Clear liquor*	*Meconium-stained or absent liquor at amniocentesis*	*Perinatal wastage*
Normal	47	42 (1)*	5	1
Low	52	31 (5)	21 (8)	13
Total	99	73 (6)	26 (8)	14

*Figures in parentheses are perinatal deaths.

Moderately severe pre-eclampsia. There were 58 patients in this category. Estriol excretion was normal in 36 patients (62 per cent) and one perinatal death occurred. There were four perinatal deaths in 22 patients with low estriol values (19 per cent). The clinical details are summarized in Tables IV, V, and VI.

In contradistinction to the group of patients with severe pre-eclampsia, 39 patients in this category (67 per cent) were managed conservatively for 2 weeks or more. In eight patients conservative treatment based on serial estriol assays was continued at least 4 weeks after the initial admission to hospital (Table IV). The indications for delivery in the 58 patients with pre-eclampsia of moderate severity who were treated conservatively between 30 and 37 weeks of gestation are summarized in Table V.

In only eight patients was the blood urea in excess of 40 mg. per 100 ml., but fetal prognosis was clearly related more closely to the estriol values than the impairment of renal function (Table VI). The average gestation at delivery in this group was 36 weeks, the average birth weight was 2,600 Gm. and the average placental weight 490 Gm.

Liquor amnii studies. The correlation between the

calculated liquor volumes, estriol levels, and perinatal outcome in the 99 patients with pre-eclampsia is shown in Table VII. In association with subnormal estriol excretion, severe oligohydramnios (< 250 ml.) was accompanied by a 35 per cent perinatal death rate and a 75 per cent incidence of intrauterine growth retardation (Table VII). Liquor volumes between 250 and 500 ml. in association with low estriol levels resulted in a 26 per cent perinatal wastage. There were no perinatal deaths where volumes in excess of 500 ml. were associated with subnormal estriol excretion.

The over-all incidence of meconium staining or absent liquor at amniocentesis prior to labor was 26.3 per cent, but was 40.4 per cent in patients with subnormal estriol values (Table VIII). In 21 patients with subnormal estriol excretion and meconium-stained or absent amniotic fluid at amniocentesis there were seven perinatal deaths (33.3 per cent). However, in 31 patients with low estriol values and clear liquor prior to labor there were also five perinatal deaths (16.1 per cent). The fact that fetal jeopardy may be present even when associated with the presence of clear liquor before 37 weeks of gestation is well established.[9]

The L/S ratio in the amniotic fluid was less than 2:1 within 1 week of confinement in 51 patients. Of the liveborn infants, 29 weighed less than 2,500 Gm. and 10 developed the respiratory distress syndrome. Two such infants died. Forty live infants were born within 1 week of the determination of a L/S ratio of 2:1 or greater. Thirteen infants weighed less than 2,500 Gm. and two developed the respiratory distress syndrome, but survived.

Relationship between perinatal wastage, estriol excretion, L/S ratio, and the induction of labor (Table IX). In 12 patients in whom estriol excretion was subnormal and there was a subsequent stillbirth, the L/S ratio was greater than 2:1 in seven. Of these, six stillbirths occurred following the spontaneous onset of labor with a L/S ratio of greater than 2:1, but in only one case of induced labor was the L/S ratio greater than 2:1. The one neonatal death in association with subnormal estriol excretion followed a spontaneous labor at 34 weeks' gestation complicated by prolapse of the cord. The urinary estriol prior to delivery was 5.8 mg. per 24 hours and the L/S ratio 1:4.

It would seem reasonable to conclude that the number of stillbirths in association with subnormal estriol excretion may have been reduced by earlier intervention. There is no evidence to show that this would have resulted in an increased neonatal death rate in view of the fact that in two thirds of such patients the L/S ratio was greater than 2:1.

Postpartum studies. At the routine postnatal examination six weeks after delivery, the blood pressure did not exceed 140/90 mm. Hg in 70 of 83 patients who attended. Five patients had persistent albuminuria. Of 66 patients in whom intravenous pyelography was performed, the investigation was normal in 60 cases. The results are summarized in Table X.

Postpartum renal biopsy was performed in 39 patients. The investigation was usually carried out 6 weeks after confinement, although in one patient with severe hematuria a biopsy was performed 1 week postpartum. This revealed acute glomerulonephritis. However, in 30 of the 39 successful renal biopsies the histologic findings either were quite normal or showed no evidence of an underlying renal disorder, but resolving pre-eclamptic changes. The results are summarized in Table XI.

On analyzing the individual case histories, it was apparent that there was generally no correlation be-

Table IX. Relationship between perinatal wastage, L/S ratio, and termination of pregnancy in 13 patients with subnormal estriol excretion

	Stillbirths	*Neonatal deaths*
Spontaneous labor	8 (6)*	1 (0)
Surgical induction of labor	4 (1)*	—
Total	12 (7)	1 (0)

*Figures in parentheses refer to patients delivered with L/S ratio >2:1 at amniocentesis.

Table X. Results obtained with intravenous pyelography in 66 patients with pre-eclampsia

X-ray finding	*No.*
Normal intravenous pyelogram	60
Chronic pyelonephritis	2
Horshoe kidney	1
Double ureter	1
Solitary kidney with pyelonephritis	1
Bilateral staghorn calculi	1

Table XI. Postpartum renal biopsy findings in 39 patients with pre-eclampsia

Histologic finding	*No.*
Resolving pre-eclamptic changes with no evidence of underlying renal disease or damage	21
Normal	9
Acute glomerulonephritis	1
Chronic pyelonephritis	2
Diffuse hypertensive nephrosclerosis	2
Sub acute/chronic glomerulonephritis	2
Focal glomerulonephritis (mild changes)	1
Nephrocalcinosis	1

tween the severity of the pre-eclampsia and the postpartum clinical or renal tract findings.

Comment

The present study clearly showed that the value of conservative treatment based essentially on serial estriol and liquor amnii assays has its greatest application in patients with pre-eclampsia of mild and moderate severity. In severe pre-eclampsia, perinatal death is as much dependant on placental function as on the period of gestation when the condition develops.

In managing patients with severe pre-eclampsia conservatively very careful monitoring of the maternal and fetal condition is mandatory. Any deterioration of the pre-eclampsia warrants termination of the pregnancy for maternal reasons. Furthermore, in this study there was a 73 per cent incidence of subnormal estriol excretion in patients with severe pre-eclampsia, which correlated closely with an unfavorable fetal outcome. Of the eight stillbirths in association with low estriol excretion in severe pre-eclampsia, the L/S ratio was greater than 2:1 in three, and earlier intervention may have resulted in a more favorable outcome.

However, in patients admitted with pre-eclampsia of moderate severity, 67 per cent were managed conservatively for 2 weeks or more, and in eight patients at least 4 weeks of gestation was gained after the initial admission to hospital.

The present study confirmed the findings of Elliott[10] and Beischer and associates[11] that fetal jeopardy is related to both severe oligohydramnios and greatly reduced estriol excretion. In association with subnormal estriol excretion, severe oligohydramnios (liquor volume < 250 ml.) was accompanied by a 35 per cent perinatal mortality rate and a 75 per cent incidence of intrauterine growth retardation. Normal or low but rising estriol levels associated with liquor volumes above 500 ml. predicted that the pregnancy could be prolonged and that perinatal deaths due to complications of prematurity avoided. Low and falling estriol values, especially if associated with severe oligohydramnios (<250 ml.), indicate the need for rapid termination of pregnancy. Such conservative treatment based on serial estriol measurements and examination of the liquor amnii has its greatest application in pre-eclamptic patients between 30 and 34 weeks of gestation, but it must not be continued where there are strong clinical contraindications.

The over-all incidence of meconium staining of the liquor amnii or failure to obtain liquor at amniocentesis was 26.3 per cent, but was 40.4 per cent in patients with subnormal estriol excretion. However, the absence of meconium in the liquor prior to or during labor was no guarantee that fetal distress was not imminent. Indeed there were six perinatal deaths in association with the presence of clear liquor amnii, and all but one were associated with low estriol values. While it may be true that the passage of meconium is usually the case in the mature fetus when subjected to hypoxia, this is certainly not the case before 37 weeks gestation.

Follow-up studies of pre-eclamptic patients. Irrespective of the severity of the pre-eclampsia, it was unusual for the patient to have either residual hypertension or proteinuria at the postnatal visit 6 weeks after delivery. Postpartum pyelography was normal in all but six of the 66 patients in whom the test was performed. The results of renal biopsy indicated either normal histology or regression of the classical glomerular lesion in 30 of the 39 patients in whom the test was performed. In the remaining nine patients the changes suggesting an underlying vascular or renal disease were usually of mild degree. Furthermore, the likelihood of discovering an underlying renal disorder at postpartum biopsy in patients with pre-eclampsia could be related to neither the severity of the disease nor the time of its occurence in the third trimester of pregnancy.

The most notable features of the renal glomerular lesion in pre-eclampsia are: (1) swelling and proliferation of endothelial cells; (2) increase in mesangial cells and matrix; both of these lead to a reduction of capillary lumina and the swollen and eschemic glomerular tuft tends to fill Bowman's space; (3) abnormal granular, fibillary, and basement membrane–like deposits between and within endothelial cells, in mesangial matrix, and in continuity with the endothelial aspect of the basement membrane.

The complete reversibility of these lesions is well established, although the process may occasionally take up to 12 months to do so.[12–13] Dieckmann and associates[12] in 1957 obtained postpartum renal biopsies from 26 primiparas and 44 multiparas with prior pre-eclampsia. Twenty-four of the primiparas showed only the classical pre-eclamptic lesion, and in two there were renal arteriosclerotic changes as well. In the 44 multiparas, underlying renal pathology was found in six cases. Fadel and associates[13] and Dyer,[14] in similar studies, reported that the glomerular lesion of pre-eclampsia was completely reversible, leaving neither residual glomerular damage nor residual hypertension. As expected, the detection of underlying renal pathology was also slightly higher in the multiparous group of patients.

The question of whether pre-eclampsia or eclampsia causes residual hypertension or renal damage has been debated for many years. This is of particular im-

portance if one is to advocate a more conservative policy based on serial estriol and liquor amnii studies in the management of the less severe pre-eclamptic patients with proteinuria before 37 weeks of gestation.

In 1964, Epstein[15] reported that approximately 33 per cent of all patients who had eclampsia or pre-eclampsia are left with permanent hypertensive vascular disease. However, virtually all other workers refute this claim and it is now fairly clear that neither subsequent hypertension nor renal pathology will follow albuminuric pre-eclampsia or eclampsia.[12, 16–22]

The two most carefully controlled studies are those of MacGillivray[20] and Chesley and associates.[21] Both reports showed that women with hypertensive tendencies or pre-existing chronic renal disease are more liable to develop pre-eclampsia during pregnancy, and that they would ultimately become hypertensive even if they never became pregnant. Pregnancy presumably reveals any latent tendency to develop hypertension in later life, and it seems fairly clear that it is the genetic predisposition of the patient with pre-eclampsia which is important. The strong familial trait in essential hypertension, pre-eclampsia, and eclampsia has long been recognized, and Zuspan[23] noted that in a 25 year follow-up of patients with eclampsia, those with hypertension after the age of 50 always had a strong family history of hypertension. Conversely, in the normotensive group of patients with previous eclampsia, there was no familial evidence of hypertension.

I wish to acknowledge the advice and encouragement given by Sir Lance Townsend, who also provided the laboratory and secretarial assistance to complete this study. The nursing and medical staff in the Professorial Unit antenatal and labor wards deserve thanks for coordinating the work involved in the many 24 hour urine collections, amniocenteses, and renal tract investigations. Most of the detailed postpartum renal tract studies were carried out under the supervision of Dr. John Dawborn in the Renal Unit at the Austin Hospital, Heidelberg.

REFERENCES

1. Michie, E. A.: J. Obstet. Gynaecol. Br. Commonw. **74:** 896, 1967.
2. Klopper, A.: Obstet. Gynaecol. Survey **23:** 813, 1968.
3. Reid, S., Beischer, N. A., Brown, J. B., and Smith, M. A.: Aus. N. Z. J. Obstet. Gynaecol. **8:** 189, 1968.
4. Booth, R. T., Stern, M. I., Wood, C., Sharples, M. J., and Pinkerton, J. H.: J. Obstet. Gynaecol. Br. Commonw. **72:** 229, 1965.
5. Müller, K., and Nielson, J. C.: Dan. Med. Bull. **14:** 165, 1967.
6. Brown, J. B., Macleod, S. C., Macnaughtan, C., Smith, M. A., and Smyth, B.: J. Endocrinol. **42:** 5, 1968.
7. Charles, D., and Jacoby, H. E.: Am. J. Obstet. Gynecol. **95:** 266, 1966.
8. Kitchen, W. H.: Aus. Paediatr. J. **4:** 29, 1968.
9. Campbell, K.: Personal communication, 1963.
10. Elliott, P. M.: Aus. N. Z. J. Obstet. Gynaecol. **7:** 13, 1967.
11. Beischer, N. A., Brown, J. B., and Townsend, L.: Am. J. Obstet. Gynecol. **103:** 496, 1969.
12. Dieckmann, W. J., Potter, E. L., and McCartney, C. P.: Am. J. Obstet. Gynecol. **73;** 1, 1957.
13. Fadel, H. E., Sabour, M. S., Mahran, M., Seifel-Din, D., and El-Mahallawi, M. N.: Obstet. Gynecol. **33:** 528, 1968.
14. Dyer, R. P.: S. Afr. J. Obstet. Gynaecol. **6:** 75, 1968.
15. Epstein, F. H.: N. Engl. J. Med. **271:** 391, 1964.
16. Theobald, G. W.: Lancet **1:** 626, 1933.
17. Barnes, J., and Browne, F. J.: J. Obstet. Gynaecol. Br. Emp. **52:** 1, 1945.
18. Adams, E. M., and MacGillivray, I.: Lancet **2:** 1373, 1961.
19. Altchek, A.: J. A. M. A. **175:** 791, 1961.
10. MacGillivray, I.: J. Obstet. Gynaecol. Br. Commonw. **68:** 557, 1961.
21. Chesley, L. C., Annitto, J. E., and Cosgrove, R. A.: Am. J. Obstet. Gynecol. **101:** 886, 1968.
22. Eastman, N. J.: Obstet. Gynecol. Survey **23:** 238, 1968.
23. Zuspan, F. P.: J. Reprod. Med. **2:** 116, 1969.

Reduction of the stretch modulus of human cervical tissue by prostaglandin E_2

JOHN T. CONRAD, PH.D.
KENT UELAND, M.D.
Seattle, Washington

Samples of cervical tissue were obtained from women immediately following term delivery from spontaneous labor or oral PGE_2-induced labor and from a small number of nonpregnant women in the reproductive years undergoing hysterectomy for benign gynecologic disease. The measured strips were placed in a well-oxygenated bath at 37° C. containing Ringer's solution and stretched at a constant rate while continuously recording length and tension. The data were converted to stress-strain diagrams. Each curve contained a long linear portion which allowed one to compute a stretch modulus for each sample. A total of 71 strips from 23 patients was used. The average stretch modulus from the oral PGE_2-induced patients was significantly lower than the spontaneous labor group ($p < 0.005$), which, in turn, was significantly lower than the stretch modulus of the nonpregnant cervical tissue. It was also noted that the yield point was lower in the PGE_2 series when compared to the spontaneous labor series ($p < 0.05$). The effect of the PGE_2 at a bath concentration of 10^{-5} to 10^{-6} Gm. per cubic centimeter was to materially reduce the stretch modulus within 5 to 15 minutes of the drug addition in both the PGE_2-induced and spontaneous labor series. The results of these experiments indicate that PGE_2 has the effect of reducing cervical stiffness.

THE PROSTAGLANDINS appear to be very potent, naturally occurring, uterine-stimulating agents. As such, there has been extensive clinical work done with these materials in various aspects of obstetrics in an attempt to utilize them for menstrual induction,[10] abortion,[6, 13] or induction of labor at term.[1]

The major thrust, however, has been to use prostaglandins for the induction of labor at term. In 1968, Karim[9] initially reported on the use of intravenous $PGF_{2\alpha}$ to induce labor at term. Many other similar clinical studies have followed and the consensus among investigators seems to be that intravenous $PGF_{2\alpha}$ is equivalent to intravenous oxytocin for induction of labor at term. The effect on uterine activity of other prostaglandins (primarily E_2) has likewise been tested by intravenous, intravaginal, intra-amniotic, oral, and extraovular routes.[1, 11, 12, 15, 19]

Although the majority of past research has been devoted to a consideration of the myometrium-stimulating effects of the prostaglandins, it has been noted that an additional role may be one of cervical softening. Dingfelder and associates[5] measured the force necessary to dilate the cervix and found that $PGF_{2\alpha}$ and PGE_2 did lower the cervical resistance in 60 nulliparas at 6 to 12 menstrual weeks of gestation. They felt that $PGF_{2\alpha}$ was effective in inducing labor in patients with clinically "unripe" cervices, possibly due to a direct but unspecified effect on the cervix. Likewise, Toppozada and associates[18] felt that dilation of the cervix by prostaglandin (15-methyl $PGF_{2\alpha}$) prior to vacuum aspiration during the first trimester was a sound clinical procedure with minor side effects.

Our own clinical experience with the use of oral PGE_2 has indicated that this agent may be more effective than oxytocin for the induction of labor near term in the presence of an "unripe" cervix. In response to

From the Department of Obstetrics and Gynecology, School of Medicine, University of Washington.

This research was supported by a grant from the Upjohn Company, Kalamazoo, Michigan.

An abstract of this paper was presented at the International Conference on Prostaglandins, May 26 to 30, 1975, in Florence, Italy.

Received for publication November 21, 1975.

Accepted February 3, 1976.

Reprint requests: John T. Conrad, Ph.D., Department of Obstetrics and Gynecology, School of Medicine, University of Washington, RH-20, Seattle, Washington 98195.

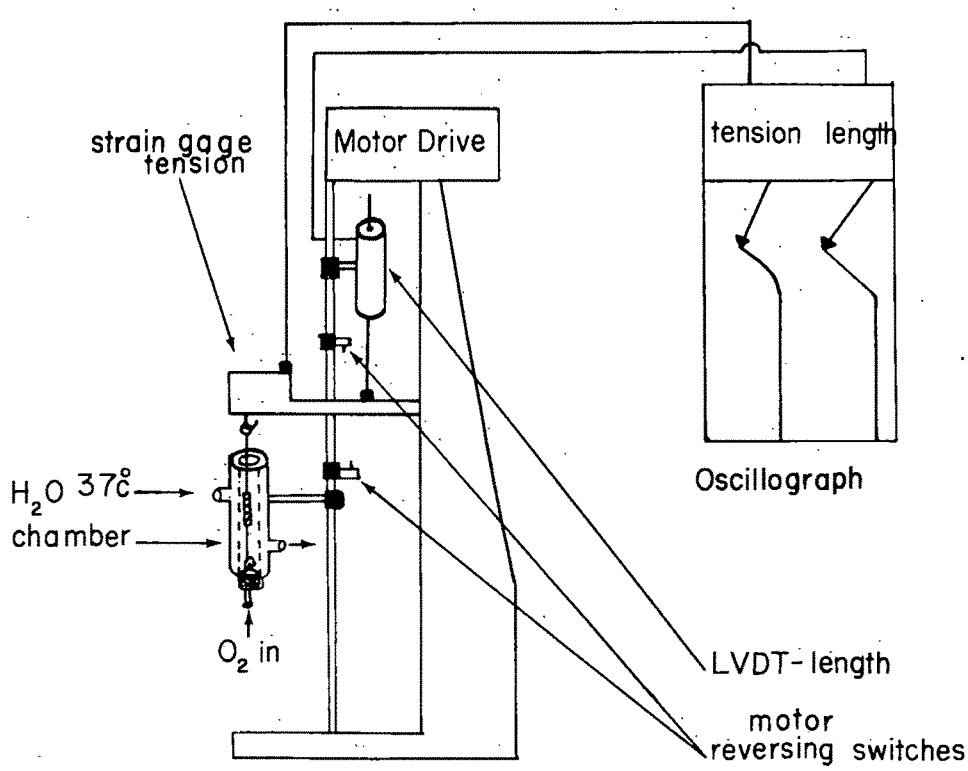


Fig. 1. Schematic diagram of the experimental apparatus used in these experiments. The LVDT (linear variable differential transformer) measures the position of the strain gage transducer, hence, the change in length. The strain gage transducer measures the tension on the strip within the chamber. A change in length is produced by the motor drive, which is reversed when the motor-reversing switches are activated by the motion of the strain gage platform. This action produces a triangular increase and then decrease in length.

this clinical observation, we have designed a simple in vitro experiment to test the effect of PGE_2 upon the elastic characteristics of the noncontractile portion of the cervix.

Materials and methods

A small cervical biopsy specimen, measuring approximately 1 by 0.5 cm., was obtained immediately following delivery of the placenta in a group of normal women. An informed consent was obtained in each case. The biopsies were removed from patients receiving oral PGE_2 for the induction of labor at term, with a variable dose regimen, and from patients who delivered following spontaneous labor. A small number of specimens were obtained from nonpregnant patients undergoing hysterectomy for benign gynecologic disease. The biopsy specimens were transferred to the laboratory, where strips were cut from the central fibrous region and measured by means of an optical micrometer for both length and cross-sectional diameter in the resting and unstressed state. Ligatures were then applied to both ends and the strips placed in a chamber, where they were mounted at the cut length. One end of the tissue was attached to a Grass FT 03 force transducer and the other end was anchored to the bottom of the chamber.

Fig. 1 illustrates the important aspects of the experimental arrangement. The chamber contains the tissue in Ringer's solution which is maintained at 37° C. by an outer jacket of circulating water. Oxygen is continously bubbled through the tissue chamber from below.

After the tissue is fixed in position, it is allowed to equilibrate for 15 to 30 minutes. The motor drive is then turned on to extend the tissue at the rate of 0.33 mm. per minute. The length of the tissue is continously sampled by a Sanborn type 7DCDT-2000 length transducer and the tension is measured with a Grass tension transducer (conditioned by a Tektronix type Q unit in a type 133 power supply), and both signals are recorded on a BLH Meterite two-channel oscillograph.

For analysis, the records were converted to stress/strain diagrams. The stress was calculated by dividing the tension by the unstressed cross-sectional area.

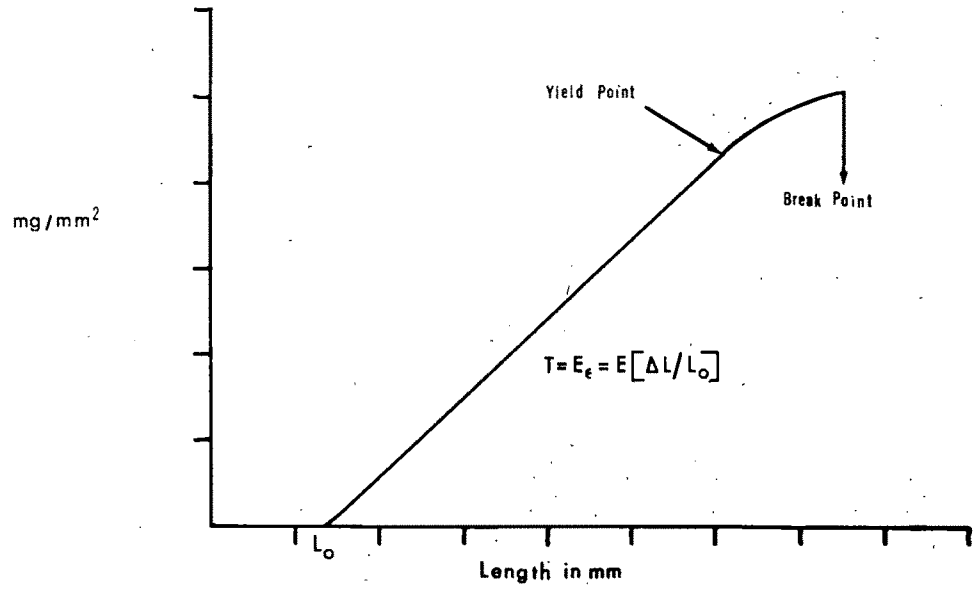


Fig. 2. An idealized stress-strain curve. L_0 is the original length of the material. T is the tension; if expressed as force/area, it is equal to $E\epsilon$, the stress, E is the stretch modulus, ΔL is the change in length, and L_0 is the length at rest. $[\Delta L/L_0]$ is the strain and is expressed as a ratio, without dimensions. At the yield point, the increase in strain does not produce an equivalent increase in stress. At the break point, the tissue ruptures.

Strain was expressed as a fraction of the original length of the specimen. The resulting curves were replotted on graph paper. Since most of the stress/strain diagrams had a very linear portion, it was possible to statistically compare the various test classes in a simple manner. The model used was that of a simple spring as shown in Fig. 2. The spring constant (i.e., stretch modulus) was calculated from the linear portion of each curve by the formula:

$$E = \frac{T/A}{\Delta L/L_0}$$

where E = stretch modulus in milligrams per millimeter,
A = unstressed sample cross section in square millimeters,
T = recorded tension in milligrams,
ΔL = elongation in millimeters,
L_0 = unstressed length in millimeters.

The use of only a linear portion of the stress-strain relationship does lead to problems in data presentation, mainly because of the fact that the classical linear theory of elasticity is strictly applicable to infinitesimal strain.[7] In addition, most biologic tissues show an elastic stress that is an approximation of an exponential function of the extension ratio. Therefore, any calculation of Young's modulus (or the stretch modulus, as in these experiments) would vary with the strain. However, the linear portion of the curve was sufficiently long in these pieces of cervix so that a single slope could be used to measure the elasticity of the sample. This allowed the authors to use a simplified, but sufficiently accurate method for numerically comparing the different groups.

Results

A. Stress-strain characteristics of cervical tissue. A typical oscillograph record, made during this experimental series, is depicted in Fig. 3. The figure includes a calculation of the stretch modulus for one strip of cervix. In this sample, the strip was not pulled to the breaking point, but the motor drive was reversed and the strip was pulled through an additional series of pulls. If the tissue is stretched repeatedly through a series of extensions and relaxations, there is a gradual decline in the peak tension with each cycle of pull. Conversely, the stretch modulus, as measured on the linear portion of the curve increased and stabilized at a higher level. As a result of this rise in the stretch modulus, the first pull was used when comparing the stretch modulus for the various groups of tissues in these experiments. The hysteresis curves formed by successive triangular extensions demonstrated a closing of the loop until it stabilized at a lower point.

When the specimen is strained to the yield point, it is found that the failure is rather gradual. This was particularly true for the specimens obtained from *term*

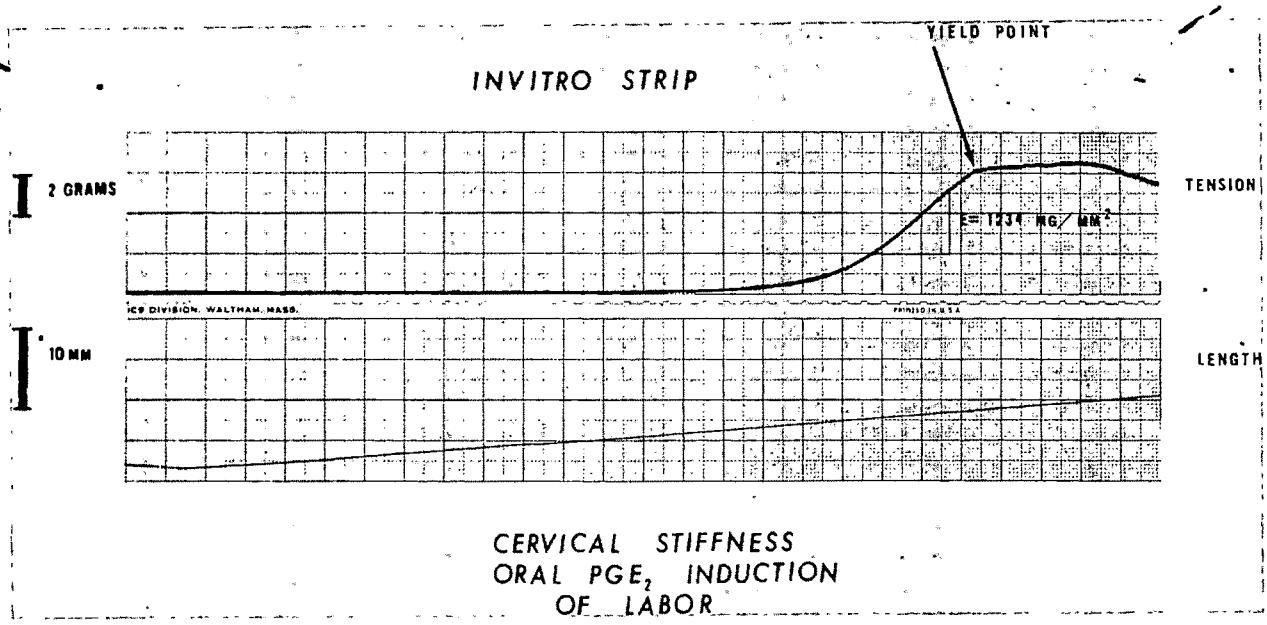


Fig. 3. The results of a typical experiment. Human cervical tissue from a term patient. A sample calculation of the stretch modulus is shown at the midportion of the tension curve.

Table I

	Spontaneous labor	*PGE_2 induction*	*t test*
Pregnant:			
Stretch modulus (mg./mm.^{2})	2,106 ± 219.5 S.E. N = 26	1,222 ± 117.4 S.E. N = 19	$p < 0.005$
Yield point (mg./mm.^{2})	2,678 ± 533.3 S.E. N = 11	1,170 ± 231.5 S.E. N = 7	$p < 0.05$
Nonpregnant:			
Stretch modulus (mg./mm.^{2})	5,558 ± 631.5 S.E. N = 8		
Yield point (mg./mm.^{2})	No yields up to 12,500		

patients. When failure finally occurs, it does so at an unpredictable point and after a relatively large strain. Quite often, the failure consists of a number of small slips in the tissue, as was especially true for the tissues removed from the PGE_2-induced patients. This appears to be the result of micro tears of the tissue without gross visible changes.

B. Comparison between samples from spontaneous labor, PGE_2-induced labor, and nonpregnant patients. As is well known clinically, the feel of the term pregnant cervix is quite different from that of the nonpregnant cervix. This was also true for the specimens obtained in this series. The tissues from pregnant patients were obviously softer to the touch and felt less fibrous when cut than the nonpregnant cervical samples.

Fig. 4 compares the representative stress-strain curves from the three classes of tissue studied. As may be seen, there is a progressive reduction in stiffness from nonpregnant to spontaneous labor to PGE_2-induced labor. As one proceeds from left to right, there is an increase in compliance (or a decrease in stiffness). There is a certain amount of overlap between the two classes of tissue from the pregnant patients. Nonetheless, the calculated stretch moduli, when compared statistically, are significantly different to $p < 0.005$ (Table I). From the table, it may be seen that the stretch moduli in the two classes of tissue from pregnant patients are significantly lower than the nonpregnant and those in the PGE_2-induced labor samples are the lowest.

In addition to the demonstrated difference in the

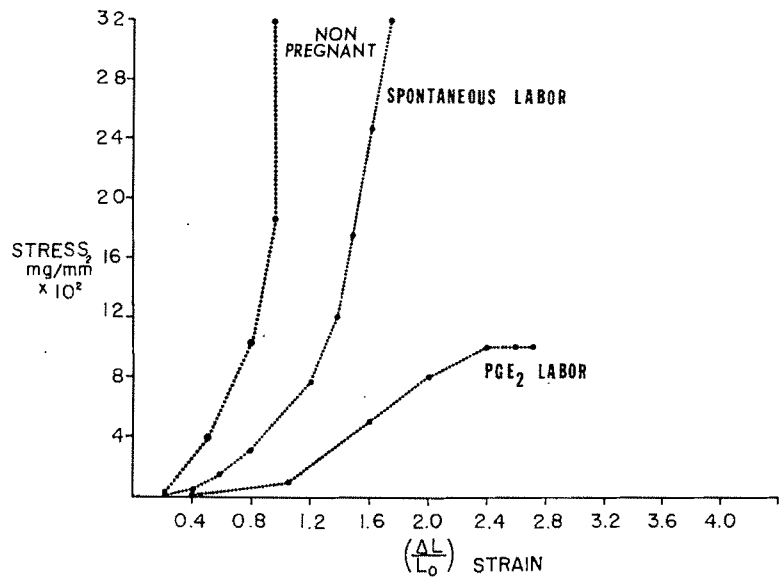


Fig. 4. Representative stress-strain diagrams of the experiments done on human cervical tissue from nonpregnant women and from women in spontaneous labor and PGE_2-induced labor, at term.

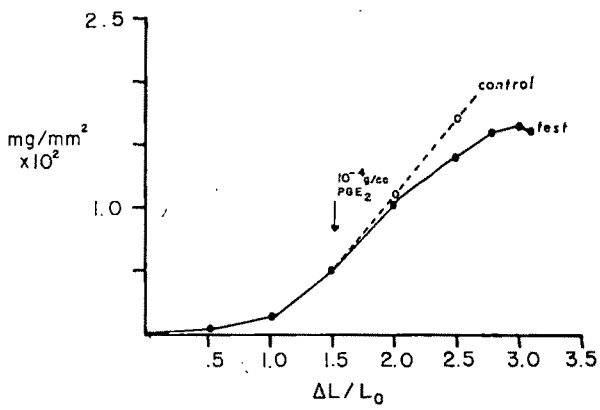


Fig. 5. The effect of in vitro addition of PGE_2 in a pair of matched cervical tissue samples. The samples were cut from adjacent pieces of tissue to the same size. The control strip was pulled without PGE_2. The test strip was pulled with the addition of 10^{-4} Gm. per cubic centimeter of PGE_2 (bath concentration) at the arrow.

stretch modulus between spontaneous and PGE_2-induced labor patients, it was also noted that the yield point appeared to be lower in the PGE_2 series (Table I). Although of less statistical significance, partly because of fewer numbers, the comparison of yield points may be physiologically important in helping one better understand cervical function. It is quite apparent that the yield points of the nonpregnant series are much higher than those of the pregnant series.

C. In vitro addition of PGE_2 (Fig. 5). The addition of PGE_2 to the bath, in most cases, resulted in a reduction of the slope of the stress-strain curve within 5 to 12 minutes. This reduction with a dose of PGE_2 ranging from 10^{-5} to 10^{-6} Gm. per cubic centimeter was compared in a series of experiments with matched pairs of strips. It was found that there was an average reduction of the stretch modulus in a series of 13 matched strips of 36.2 per cent and of the yield point of 48.4 per cent in the five cases where this was determined. The matched strips consisted of one pulled without PGE_2 and the other pulled in the presence of the drug. Strips from both spontaneous labor and PGE_2-induced labor patients were used in this series of experiments.

Comment

There appears to be a dual role of the cervix during pregnancy.[14] On the one hand, it remains closed during pregnancy to retain the conceptus, whereas during labor it dilates and effaces to allow birth to occur.

What keeps it closed during most of pregnancy and the mechanism by which it effaces and dilates during labor are unknown and speculative. There appear to be two schools of thought. (1) Cervical effacement and dilatation result from the stretching induced by coordinated uterine contractions.[8] The cervix is thought to be an active participant in dilatation by virtue of an interplay between the contractions of the outer extrinsic cervical muscle layer and the upper cervical muscle layer. The inner core of the cervix is passive. The separation of the collagen by fluid during pregnancy allows the two muscle layers to contract and enhance dilation without the excessive damping of the tension

by dense collagen. (2) Danforth,[3, 4] on the other hand, perceives the cervix as essentially a dense fibrous connective tissue structure. Effective labor converts this into a tissue that has separated and scattered collagen material. This separation takes place as a result of an increase in water, a decrease in collagen and glycoprotein and a marked increase in glycosaminoglycans. In addition,[4] a new component has been isolated, of an unidentified nature, which indicates that dynamic changes are occurring in the cervix during dilatation. Cervical dilatation is thus controlled mainly by uterine activity interacting with a greatly reduced resistance to stretch of the cervix as a result of biochemical changes, which in turn, alters its physical properties.

The results of this study support the findings of Danforth to the extent that marked changes in the mechanical behavior of the fibrous core of the cervix take place during dilatation. These elastic alterations are enhanced by the prostaglandin E_2 and give evidence to the fact that cervical supportive tissues change during labor. That they are not changes due to contraction of intrinsic muscle may be seen in the facts that: (1) only the dense collagenous central core of the cervix was used in these experiments; Hughesdon[8] has made the observation that muscle is confined to the outer layer of the cervix; and (2) in only one instance was anything that could be conceived as a contraction observed in these studies. The particular strip in question was removed from a more outer layer of the cervix and it did demonstrate some degree of contractility. The tension output of this strip was very low, only about 58 mg. per square millimeter, as compared to 800 to 1,600 mg. per square millimeter for human uterine muscle,[2] indicating that the active muscle in this strip comprised less than 10 per cent of the muscle mass found in uterine muscle. This observation agrees with the histologic and biochemical study of Rorie and Newton.[17]

Studies of the contractile ability of the nonpregnant cervix have been made by Najak and associates[16] in vitro. They found that the nonpregnant cervix showed spontaneous contractility and these strips responded to $PGF_{2\alpha}$ by variable contractions and to PGE_2 by relaxation. The effect on the cervix of the pregnant patient was not tested. However, in their study only the outer contractile layer was used and the results are not applicable to the present study in which only the elastic core of the cervix was used.

The fact that the prostaglandin E_2 does reduce the connective tissue stiffness in the term pregnant cervix adds to the clinical efficacy of this drug, suggesting, perhaps, that it may be a more effective agent for indicated inductions of labor when the cervix is unfavorable. Since labor is a combination of contractions of uterine muscle and dilatation of the cervix, a drug that favorably affects both modalities is of greater use than a uterine stimulant alone.

The majority of research into the reproductive aspects of the prostaglandins has been directed toward their actions as oxytocic agents, while little emphasis has been placed on softening effects on the cervix. These data suggest that PGE_2 has a favorable effect on the pregnant cervix but further studies are clearly needed to further define this very important clinical entity.

REFERENCES

1. Anderson, G. G.: Prostaglandins **4:** 765, 1973.
2. Conrad, J. T., and Kuhn, W., Am. J. Obstet. Gynecol. **97:** 154, 1967.
3. Danforth, D. N.: Am. J. Obstet. Gynecol. **53:** 541, 1947.
4. Danforth, D. N., Veis, A., Breen, M., Weinstein, H. G., Buckingham, J. C., and Manalo, P.: Am. J. Obstet. Gynecol. **120:** 641, 1974.
5. Dingfelder, J. R., Brenner, W. E., Hendricks, C. H., and Stavrovsky, L. G.: Am. J. Obstet. Gynecol. **122:** 25, 1975.
6. Freid, N. D., Tredway, D. R., and Mishell, D. R.: Contraception **8:** 255, 1973.
7. Fung, Y. C. B.: Am. J. Physiol. **213:** 1532, 1967.
8. Hughesdon, P. E.: J. Obstet. Gynaecol.. Br. Commonw. **59:** 763, 1952.
9. Karim, S. M. M.: Br. Med. J. **4:** 621, 1968.
10. Karim, S. M. M.: Contraception **3:** 173, 1971.
11. Karim, S. M. M.: J. Reprod. Fertil. **16:** 105, 1972.
12. Karim, S. M. M., and Hillier, K.: Res. Prostag. **2:** 1, 1973.
13. Karim, S. M. M., and Sharma, S. O.: J. Obstet. Gynaecol. Br. Commonw. **78:** 294, 1971.
14. Lindgren, L.: *In* Blandau, R. J., and Moghissi, K., editors: The Biology of the Cervix, Chicago, 1973, Univ. of Chicago Press.
15. Naftolin, F.: *In* Kahn, R. H., and Lands, W. E. M., Editors: Prostaglandins and Cyclic AMP, New York, 1973, Academic Press Inc.
16. Najak, Z., Hillier, K., and Karim, S. M. M.: J. Obstet. Gynaecol. Br. Commonw. **77:** 701, 1970.
17. Rorie, D. K., and Newton, M.: Am. J. Obstet. Gynecol. **99:** 466, 1967.
18. Toppozada, M., Bygdeman, M., Papageorgiou, C., and Wiqvist, N., Prostaglandins **4:** 371, 1973.
19. Wentz, A. C., Thompson, B. H., and King, T. M.: Am. J. Obstet. Gynecol. **115:** 1107, 1973.

Spontaneous contractility and the response of the human uterine cervix to prostaglandins $F_{2\alpha}$ and E_2 during the menstrual cycle

ELSIMAR M. COUTINHO, M.D.
ELIAS DARZÉ, M.D.
Salvador, Bahia, Brazil

The effect of prostaglandins E_2 and $F_{2\alpha}$ on the contractility of the uterine cervix was investigated in nonpregnant women throughout the menstrual cycle. $PGF_{2\alpha}$ was found stimulatory to the cervix at all phases of the menstrual cycle, whereas PGE_2 was inhibitory. The relaxing effect of PGE_2 was most marked during midcycle.

ALTHOUGH THE uterine cervix is endowed with only scant muscular tissue, it is capable of developing contractile activity.[1, 2] In vitro studies with strips of the outer layer of nongravid cervices revealed that cervical muscle not only develops spontaneous motility but also responds to drugs.[3, 4] Prostaglandins E_2 and $F_{2\alpha}$ and oxytocin added to the muscle bath induced changes in tone, amplitude, and frequency of contractions. Prostaglandin E_2 inhibited, whereas oxytocin and $PGF_{2\alpha}$ stimulated contractility of the strips.[3, 4] On the other hand, in vivo studies in pregnant women suggest that cervical relaxation may be induced by intravenous infusions of either PGE_2 or $PGF_{2\alpha}$. Recently, 15-methyl $PGF_{2\alpha}$ has been used to induce cervical dilation prior to vacuum aspiration abortions.[5] In view of the relaxing effect of PGE_2, it has been suggested that this prostaglandin plays a role in facilitating sperm penetration into the uterus and also in inducing cervical effacement during parturition. In the present study we have investigated the effect of prostaglandins E_2 and $F_{2\alpha}$ on intracervical pressure throughout the menstrual cycle.

From the Maternidade Climério de Oliveira, Federal University of Bahia.

Supported by the Ford Foundation and the World Health Organization.

Received for publication December 9, 1975.

Accepted January 20, 1976.

Reprint requests: Dr. E. Coutinho, Maternidade Climerio de Oliveira, Federal University of Bahia, Salvador, Bahia, Brazil.

Material and methods

Cervical mechanical activity and response to the prostaglandins were recorded in 12 regularly menstruating women. The activity of both the cervix and of the remainder of the uterus was monitored through the recording of intraluminal pressure with elongated latex balloons of 0.5 ml. capacity. The catheters, tied together 2 cm. apart with nylon sutures, in order to prevent independent displacement of the balloons, were inserted into the uterus in such a way as to allow the cervical balloon to be retained between the internal and external os.

Prostaglandins E_2 and $F_{2\alpha}$* were injected intravenously at approximately 20 minute intervals.

Results

Spontaneous cervical motility was recorded during both the proliferative and the secretory phases of the menstrual cycle. During the proliferative phase from day 6 or 7 up to day 16 or 17, cervical activity was characterized by a high frequency of contractions of small amplitude. During the secretory phase, the rate of contractions was slower but the amplitude was greater than during the proliferative phase. During menstruation, from day 1 to day 5, almost no cervical activity could be detected. The response to prostaglandins E_2 and $F_{2\alpha}$ could be recorded in the uterus but not in the cervix during this phase. During both the proliferative and the luteal phases a cervical response to prostaglandins was recorded. Whenever a response

*Upjohn Company, Kalamazoo, Michigan.

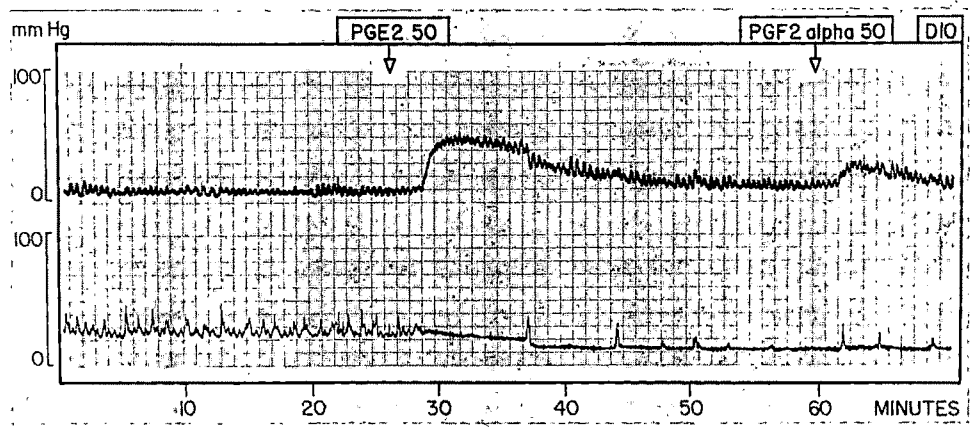


Fig. 1. The response of the human uterus and uterine cervix to prostaglandins $F_{2\alpha}$ and E_2 during the preovulatory phase. Note the stimulating effect of both PGE_2 and $PGE_{2\alpha}$ on the uterus. Note also the long-lasting relaxing effect of PGE_2 on the uterine cervix. Upper tracing: Intrauterine pressure; lower tracing: intracervical pressure.

to $PGF_{2\alpha}$ was recorded it was a stimulatory response. The effect of PGE_2, on the other hand, was invariably relaxant to the cervix but stimulatory to the remainder of the uterus. Both inhibition of cervical contractility and activation of uterine motility induced by PGE_2 was most marked during the preovulatory phase. This is shown in Fig. 1 where long-lasting inhibition of cervical motility is recorded following the administration of PGE_2.

The occurrence of spontaneous motility was not a prerequisite to obtain a pharmacologic response to prostaglandins. However, in those cervices in which no spontaneous activity occurred, the response to prostaglandins was poor or absent.

Comments

The present study confirms previous observations that the cervix is capable of developing spontaneous contractility independent of that of the uterus.[1–3] The study also confirms in vitro observations that cervical contractility is stimulated by $PGF_{2\alpha}$ and inhibited by PGE_2.[3, 4] The present observations indicate that the relaxing effect of PGE_2 on the cervix is a direct one. The relaxing effect postulated for $PGF_{2\alpha}$ infusions on the cervix of pregnant women, on the other hand, is probably an indirect effect resulting from chronic activation of uterine contractility. It is possible that PGE_2 produced locally by the contracting uterus is, in fact, the agent which causes cervical dilation in these cases.

The effect of PGE_2 on the uterine cervix may be of great physiologic significance. In fact, the effects of PGE_2 on the various segments of the female genital tract appear to be specifically aimed at facilitating the penetration and ascent of sperm. PGE_2, which is present in semen, induces relaxation of the uterine cervix, activation of uterine contractility, and relaxation of the Fallopian tube.[6] The effects of PGE_2 on the tubal isthmus and uterine cervix may indeed be prerequisites for sperm penetration since both the uterine cervix and the tubal isthmus have their internal diameter considerably reduced under the influence of estrogen, which is the dominating hormone during the preovulatory and ovulatory phases of the menstrual cycle.

REFERENCES

1. Danforth, D. N.: Distribution and functional activity of the cervical musculature, Am. J. Obstet. Gynecol. **68:** 1261, 1954.
2. Hughesden, P. E.: Fibromuscular structure of the cervix and its changes during pregnancy and labour, J. Obstet. Gynaecol. Br. Emp. **59:** 763, 1952.
3. Hillier, K., and Karim, S. M. M.: The human isolated cervix: A study of its spontaneous motility and responsiveness to drugs, Br. J. Pharmacol. **40:** 576P, 1970.
4. Schild, H. O., Fitzpatrick, R. J., and Nixon, W. C. W.: Activity of the human cervix and corpus uteri: Their response to drugs in early pregnancy, Lancet **1:** 250, 1951.
5. Toppozada, M., Bygdeman, M., Papageorgiou, G., and Wiqvist, N.: Administration of 15-methyl-prostaglandin $F_{2\alpha}$ as a preoperative means of cervical dilation, Prostaglandins **4:** 371, 1973.
6. Coutinho, E. M., and Maia, H.: The contractile response of the human uterus, fallopian tube and ovary to prostaglandins in vivo, Fertil. Steril. **22:** 539, 1971.

Bacteriologic effects of prophylactic antibiotics in cesarean section

RONALD S. GIBBS, M.D.
ALLAN J. WEINSTEIN, M.D.
Philadelphia, Pennsylvania

An eight-hour course of prophylactic clindamycin and gentamicin was given to 54 service patients undergoing cesarean section. Aerobic and anaerobic endometrial cultures obtained from eight patients who developed endometritis after prophylaxis revealed major changes in flora. Compared to infected patients who had received no prophylaxis, the clindamycin-gentamicin group had marked decreases in aerobic and anaerobic cocci and Bacteroides but increases in E. coli *and enterococci. However, this regimen was found to be no more effective than the previously reported regimen of ampicillin and kanamycin.*

A NUMBER OF STUDIES have reported significant decreases in febrile morbidity by employing prophylactic antibiotic regimens in cesarean section.[1–7] In the groups receiving prophylaxis, however, postoperative infection still occurred in 8.8 to 25 per cent of patients, and it is not clear what organisms are pathogenic in these infections. In this investigation, an eight-hour perioperative course of two potent antibiotics—clindamycin and gentamicin—was used to assess not only the clinical efficacy but also the bacteriologic effects.

Methods

The study group consisted of patients on the Obstetrical Service of the Hospital of the University of Pennsylvania. Each patient received 600 mg. of clindamycin intravenously and 80 mg. of gentamicin intramuscularly immediately prior to and eight hours after cesarean section. Patients who had received any other prophylactic regimen, who had fever in labor, or who had an allergy to either drug were excluded. In this phase of our investigations on prophylactic antibiotics, no untreated patients were included to serve as controls. Maternal, cord, and neonatal venous blood levels and amniotic fluid levels of these agents were determined and are reported elsewhere.[8] The endometrium of patients who developed fever was cultured by an aspiration technique, and samples were cultured thoroughly for aerobes and anaerobes, by techniques previously reported.[9] Endometrial cultures were not obtained from uninfected patients who received prophylaxis.

Semiquantitative bacterial colony counts were made by the method of Rotherham and Schick.[10] Light, moderate, and heavy growths correlated with colony counts of 10^3 to 10^4, 10^5 to 10^6, and greater than 10^7 colonies per milliliter, respectively.

Each patient's course was evaluated for morbidity by previously established criteria[3]: (1) a temperature $\geq$100.4° F. orally during two separate 24 hour periods, after the first 24 hours post partum; or (2) a urine culture revealing >100,000 organisms per milliliter of pathogenic organism.

Results

During the period from January 1 to May 15, 1974, a total of 54 patients met the criteria for entrance into the study. Table I shows the clinical profile of the patients, who were similar to patients studied in our previous investigations, particularly with regard to the incidence of rupture of the fetal membranes. Table II summarizes the morbidity, by type and by operation. No patient developed a wound or pulmonary infection or enterocolitis.

In Table III are shown the organisms recovered from the endometrium of eight patients who developed clinical endometritis after receiving clindamycin-gentamicin prophylaxis. For comparison, the table also shows the organisms recovered by the

From the Department of Obstetrics and Gynecology and the Department of Medicine, Infectious Disease Section, University of Pennsylvania School of Medicine.

Received for publication October 20, 1975.

Accepted December 16, 1975.

Reprint requests: Dr. Ronald Gibbs, Department of Obstetrics and Gynecology, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, Texas 78284.

same technique, during the same interval from 27 patients who developed endometritis but who had received no prophylaxis. Nine of these 27 were delivered by cesarean section, and 18 were delivered vaginally. The detailed microbiologic findings in these patients have been reported previously.[9]

In the group receiving clindamycin and gentamicin, there were significant decreases in aerobic streptococci (excluding enterococci) (chi square = 9.9; $p < 0.002$) and anaerobic cocci (chi square = 8.5; $p < 0.004$). The decrease in the Bacteroides species was striking but did not reach statistical significance (chi square = 3.0; $p = 0.08$). The concomitant increase in *E. coli* was significant (chi square = 7.0; $p = 0.008$), and the increase in enterococci was again striking but also did not reach statistical significance (chi square = 3.16; $p = 0.078$).

Antimicrobial sensitivity tests were performed on all enterococci and *E. coli* cultured from the patients who received prophylaxis. The four enterococci were, as expected, all resistant to gentamicin and lincomycin (similar to clindamycin), and the five *E. coli* were all sensitive to gentamicin. The single Klebsiella isolate was sensitive to gentamicin.

Three other patients developed urinary infections as the source of fever. In two cases, the organism was the enterococcus, and in the third it was *E. coli*.

Case summaries of the 11 morbid patients are presented in Table IV. In retrospect, it might be argued that in Patients T. G. and V. G. endometritis should not be diagnosed, but rather the diagnosis should be fever of unknown origin in view of the cultures. However, in both cases, the primary physicians believed that clinically the diagnosis was endometritis, and we have elected to report these diagnoses. Selection of antibiotics in treating these infections was not part of the protocol, but was determined by the resident evaluating the patient. In nine patients, ampicillin (to which the four enterococci and five *E. coli* were sensitive) was used initially either alone or in combination with other drugs. Patient L. J. became afebrile without specific therapy for enterococci, and Patient F. B. became afebrile without antibiotic therapy. The bacteriuria was treated after discharge from the hospital.

The efficacy of this regimen was compared to that of ampicillin-kanamycin and to a placebo from our previous studies performed under similar conditions, with a similar patient population, resident staff, and evaluation techniques.[3, 5] In the previous investigations, 39 of 62 (63 per cent) patients who received placebos and 17 of 67 (25 per cent) patients who received ampicillin-kanamycin in a double-blind study became morbid. This difference was significant (chi square = 10.47; $p < 0.002$). There was no significant difference between the febrile morbidity of the clindamycin-gentamicin group versus that of the ampicillin-kanamycin group (chi square = 0.423; $p > 0.5$), but the clindamycin-gentamicin regimen was significantly better than the placebo (data from our previous studies) in decreasing morbidity (chi square = 20.90; $p < 0.0005$).

Table I. Clinical profile of patients given clindamycin and gentamicin

Parameter	*No. of patients*	
No.	54	
*No. with ROM**	23	
Average duration of ROM		12.7 hours
No. with ROM >12 hours		9
No. without ROM	31	
No. in labor	35	
Average duration of labor		9.9 hours
No. not in labor	19	
No. having primary cesarean section	36	
No. having repeat cesarean section	18	
Hospital stay (postoperative days)	6.6	

*ROM = Rupture of membranes.

Table II. Morbidity of patients given clindamycin and gentamicin

	Total	*Primary cesarean section*	*Repeat cesarean section*
Endometritis	8	6	2
Urinary tract infection	3	3	0
Total No. morbid patients	11	9	2
Total No. patients	54	36	18
Per cent morbidity	20.4	25	11.1

Table III. Bacteria recovered from the endometrium of patients with endometritis

Bacteria	*No prophylaxis (No. = 27)*	*CL-GM* (No. = 8)*
Gram positive		
Aerobic streptococci (excluding enterococci)	17	0†
Enterococci	5	4
Anaerobic cocci	19	1†
S. aureus	3	0
Clostridia	3	0
Gram negative		
E. coli	4	5†
Klebsiella	1	1
P. mirabilis	2	0
Bacteroides	8	0
Total bacterial species	62	11

*CL = Clindamycin; GM = gentamicin.
†$p < 0.05$.

Table IV. Analysis of morbid patients

Case No.	*Patient*	*Maximum temperature*	*Endometrial culture*	*Urine culture*	*Clinical diagnosis*	*Treatment*
1	M. R.	100.6° F.	Light *E. coli*	No growth	Endometritis	Ampicillin
2	L. J.	102.6° F.	Moderate *E. coli* Moderate enterococci	14,000 enterococci	Endometritis	Cephalothin Kanamycin Tetracyline
3	P. G.	102.4° F.	Many *E. coli* Moderate enterococci	<10,000 organisms	Endometritis	Ampicillin Gentamicin Clindamycin
4	C. G.	102.6° F.	Light enterococci Light *E. coli* Light S. epi	12,000 enterococci	Endometritis	Ampicillin Clindamycin
5	T. G.	101.2° F.	No growth	No growth	Endometritis*	Ampicillin
6	M. D.	103° F.	Moderate Klebsiella Light enterococci	30,000 enterococci	Endometritis	Ampicillin Kanamycin Clindamycin
7	V. G.	101° F.	Candida sp.†	No growth	Endometritis*	Ampicillin Kanamycin
8	J. R.	100.4° F.	Light peptococci Light *E. coli* Moderate diphtheroids Moderate *S. epidermidis*	No growth	Endometritis	Ampicillin
9	C. G.	101.4° F.	No growth	>100,000 enterococci	Urinary tract infection	Ampicillin
10	F. B.	100.6° F.	Not done	>100,000 enterococci	Urinary tract infection	Not treated
11	M. A.	102.2° F.	Not done	>100,000 *E. coli*	Urinary tract infection	Ampicillin

*See text.

†Receiving ampicillin at time of culture.

Comment

The important finding in this clinical investigation was the change in endometrial flora after only two doses of clindamycin and gentamicin. Forty to 96 hours after the administration of the last dose, the endometrial bacteria in infected patients consisted almost entirely of enterococci (which were resistant to both clinadamycin and gentamicin) and *E. coli* (which were all sensitive to gentamicin). Nearly all clindamycin-sensitive organisms were eliminated. Of three urinary infections, enterococci was responsible for two, and *E. coli* was the cause of one.

Previous studies with the use of other prophylactic antibiotic regimens in cesarean section have not reported such striking changes, even though the antibiotic course was often longer.[1–7]

After a three-day course of penicillin and kanamycin, for example, Morrison and colleagues[4] reported no resistant microorganisms in their infected patients, but they did not elaborate on what organisms they did recover.

From this service, previous papers[3, 5] on perioperative antibiotics (penicillins and kanamycin) reported on 19 organisms from infected genital tracts. Encompassing the usual array of pelvic pathogens, the recovered bacteria included only two which were resistant to the regimen. Using cephalosporins for five days, Moro and Andrews[6] confirmed these findings. In 74 patients given prophylactic antibiotics, there were two cases of endometritis, both reported to be caused by sensitive *E. coli.*

Two other studies reported more frequent isolations of resistant bacteria. Employing ampicillin prophylaxis for six days, Miller and Crichton[1] did find nine of 17 (53 per cent) urinary pathogens from the antibiotic group to be resistant to ampicillin but so were 41 per cent of urinary pathogens in the control group. Only one case of endometritis in 150 patients receiving prophylaxis was noted. The pathogenic organism was reported to be a penicillinase-producing staphylococcus, resistant, of course, to ampicillin. Of eight control patients with genital tract infection, two had organisms resistant to ampicillin.

In a study with the use of cephalothin and kanamycin for 48 hours,[7] only one of 31 patients in the prophylaxis group developed endometritis. The organism was a Klebsiella, which was resistant to both antibiotics. The other two morbid patients in the antibiotic group developed wound infections. In one of these, the organism was enterococcus, resistant again to

both antibiotics. In the other wound infection, the organism was a sensitive *S. epidermidis.*

From these previous studies, it would be difficult to draw any definite conclusions on the bacteriologic effects of prophylactic antibiotics. First, the total number of organisms reported is relatively small, and second there is a paucity of anaerobes even among control patients. Any study intending to evaluate such bacteriologic effects would have to consider the presence of *B. fragilis,* a strict anaerobe which is resistant to all antibiotics used in previous prophylactic regimens. Nevertheless, organisms recovered thus far have all been usual pelvic inhabitants, nearly all of which have been sensitive to the prophylactic antibiotics.

The apparent efficacy of perioperative clindamycin in eliminating sensitive organisms is a unique, preliminary observation. If prophylactic antibiotics in cesarean section are to be used, further prospective, systematic microbiological studies are needed.

Despite this observation, use of clindamycin for prophylaxis does not appear justified. Infections after clindamycin-gentamicin prophylaxis seem to occur just as frequently as do infections after ampicillin-kanamycin. Indeed, clindamycin, presently the drug of choice for *B. fragilis* infections, should be reserved for instances when this organism is suspected as a primary pathogen. It is interesting that a clindamycin-kanamycin combination has been found to offer no advantage over penicillin-kanamycin as initial therapy in treating obstetric and gynecologic patients with severe infection. The advantage of the clindamycin-kanamycin regimen in treating *B. fragillis* was offset by its disadvantage in not treating enterococci.[11]

Conclusions

Endometrial cultures on infected patients who had received two-dose clindamycin-gentamicin prophylaxis for cesarean section revealed major changes in flora. In the prophylaxis group, there were striking decreases in aerobic streptococci (except entercocci), anaerobi cocci, and Bacteroides, but there were striking increases in *E. coli* and enterococci. All five *E. coli* were sensitive to gentamicin, and the four enterococci were resistant to both antibiotics.

Attempts to analyze previous prophylaxis studies for bacteriologic effects are hindered by the small number of organisms and paucity of anaerobic organisms. Most organisms recovered have been sensitive to the antibiotic regimen, but some resistant organisms were found in occasional patients.

Use of clindamycin for prophylaxis does not seem justified because the clindamycin-gentamicin regimen was not more effective than the ampicillin-kanamycin prophylaxis. Presently the drug of choice for *B. fragillis,* clindamycin would seem best used when this organism is a suspected primary pathogen.

REFERENCES

1. Miller, R. D., and Crichton, D.: Ampicillin prophylaxis in cesarean section, S. Afr. J. Obstet. Gynecol. **6:** 69, 1968.
2. Weissberg, S. M., Edwards, N. L., and O'Leary, J. A.: Prophylactic antibiotics in cesarean section, Obstet. Gynecol. **38:** 290, 1971.
3. Gibbs, R. S., DeCherney, A. H., and Schwarz, R. H.: Prophylactic antibiotics in cesarean section: A double-blind study, Am. J. Obstet. Gynecol. **114:** 1048, 1972.
4. Morrison, J. C., Coxwell, W. L., Kennedy, B. S., Schreier, P. C., Wiser, W. I., and Fish, S. A.: Use of prophylactic antibiotics in patients undergoing cesarean section, Surg. Gynecol. Obstet. **136:** 425, 1973.
5. Gibbs, R. S., Hunt, J. E., and Schwarz, R. H.: A follow-up study on prophylactic antibiotics in cesarean section, Am. J. Obstet. Gynecol. **117:** 419, 1973.
6. Moro, M., and Andrews, A.: Prophylactic antibiotics in cesarean section, Obstet. Gynecol. **44:** 688, 1974.
7. Rothbard, M. J., Mayer, W., Wystepek, A., and Gordon, M.: Prophylactic antibiotics in cesarean section, Obstet. Gynecol. **45:** 421, 1975.
8. Weinstein, A. J., Gibbs, R. S., and Gallagher, M.: Placental transfer of clindamycin and gentamicin in term pregnancy, Am. J. Obstet. Gynecol. **124:** 688, 1976.
9. Gibbs, R. S., O'Dell, T. N., MacGregor, R. R., Schwarz, R. H., and Morton, H.: Puerperal Endometritis: A prospective microbiologic study, Am. J. Obstet. Gynecol. **121:** 919, 1975.
10. Rotherham, E. B., and Schick, S.: Nonclostridial anaerobic bacteria in septic abortion, Am. J. Med. **46:** 80, 1969.
11. Ledger, W. J., Kriewall, T. J., Sweet, R. L., and Fekety, F. R.: Use of parenteral clindamycin in the treatment of obstetric-gynecologic patients with severe infections, Obstet. Gynecol. **43:** 490, 1974.

Abnormal adolescent primiparous pregnancy: Association of race, human chorionic somatomammotropin production, and smoking

DOROTHY R. HOLLINGSWORTH, M.D.
RUSSELL J. MOSER, PH.D.
JAY W. CARLSON, B.S.
KATHRYN T. THOMPSON, B.A.
Lexington, Kentucky

Abnormal pregnancies (33 per cent) were studied in 417 consecutive, unmarried, primiparous women, age 12 to 18 years (black, 54 per cent; white, 46 per cent). Black patients had no increase in abnormal pregnancies but had more infants weighing <2,500 grams ($p < 0.01$). Black patients with pre-eclampsia gained less weight than white patients (24 versus 34 pounds, $p < 0.05$) and had smaller infants (2,834 versus 3,316 grams). In white patients, the mean age at menarche was earlier in women who lost their infants (11.0 versus 12.7 years; $p < 0.01$). Smoking was more prevalent in normal pregnancies (47 per cent) than abnormal pregnancies (38 per cent). Spontaneous abortion and fetal loss occurred more often in smokers ($p < 0.01$). White women smoked more than blacks (60 versus 37 per cent). In mothers of infants weighing <2,500 grams, there were fewer smokers. Unexpectedly, smokers had less hypertension and pre-eclampsia. Human chorionic somatomammotropin values correlated with infant size. Levels of <4 μg per milliliter after 30 weeks' gestation were identical in normal and abnormal pregnancies (4.4 per cent). They were associated with small infants but no fetal deaths and did not predict outcome of pregnancy.

ADOLESCENT PRIMIPAROUS women are recognized as a high-risk obstetric group.[1–5] In this three-year prospective study, 417 consecutive women were evaluated. A previous report described findings in normal adolescent primiparous pregnancy in 252 patients.[6] Those who failed to meet the criteria of Spellacy and associates[7] for normal pregnancy are reported here.

In this more extensive experience, 135 young women, 12 to 18 years old (33 per cent of total population) with the following pregnancy complications were investigated: (1) pre-eclampsia (11 per cent), (2) infant <2,500 grams (9 per cent), (3) maternal hypertension (7 per cent), (4) spontaneous abortion and fetal loss (5 per cent), (5) infant >4,000 grams (3 per cent), and (6) diabetes (0.5 per cent). Race, smoking, and human chorionic somatomammotropin (HCS) production were compared in normal and abnormal pregnancies.

From the Department of Pediatrics, University of Kentucky.

Supported by Grants Nos. 25019 and 25099 from the University of Kentucky Tobacco and Health Research Institute and Grant S3183 from the Kentucky Department of Maternal and Child Health.

Received for publication October 21, 1975.

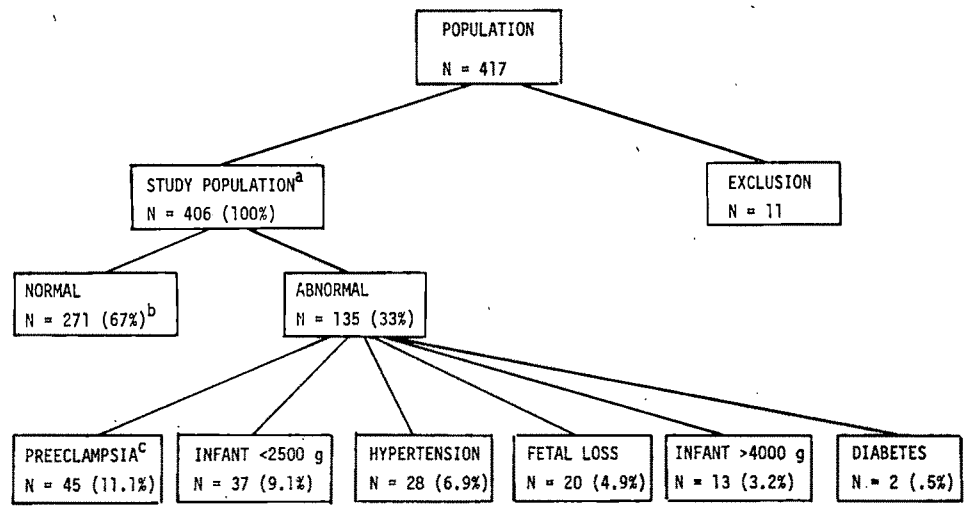
Revised December 10, 1975.

Accepted December 12, 1975.

Reprint requests: Dr. Dorothy R. Hollingsworth, Department of Pediatrics, University of Kentucky, Lexington, Kentucky 40506.

Material and methods

Study population. Four hundred and seventeen adolescent women were admitted from 1971 to 1974 to the University of Kentucky "Young Mother's Program," a combined medical-obstetric service for girls between the ages of 12 and 18 years who were pregnant for the first time (Fig. 1). Five women with pregnancies resulting in twins, four women later found to be in their second pregnancy, one nonpregnant woman, and one woman who had a therapeutic abortion were excluded from the data analysis. Of the 406 remaining patients, there were 219 black women (54



[a]The study population contained 219 black (54%) and 187 white (46%) patients.
[b]All percentages based on study population.
[c]Abnormal subgroups are not always mutually exclusive.

Fig. 1. Pregnancy outcome in 417 consecutive adolescent pregnancies in women 12 to 18 years old.

per cent) and 187 white women (46 per cent) from families with incomes ranging from zero to $24,000 per year (mean, $4,200). The mean annual income for black families ($3,629) was lower than that for white families ($4,900). The low socioeconomic status of black and white patients, as evaluated by place of residence, was comparable in this medium-sized urban area (population 200,000) consisting of 88 per cent white and 12 per cent black.

Data collection and description. All patients had the usual clinic obstetric care including a complete history, physical examination, and appropriate laboratory studies. Each patient was interviewed by the project dietitian and assigned a diet grade of excellent, good, fair, or poor on the basis of a point system devised according to intake of the four major food groups.

The criteria followed for classification of hypertension and pre-eclampsia were those recommended by the American Committee of Maternal Welfare as tentatively revised by the American College of Obstetricians and Gynecologists.[8]

All patients were interviewed in the clinic by an interviewer using the smoking history interview schedule.[9] Patients who smoked during pregnancy were classified as smokers. Patients who did not smoke during pregnancy but had smoked previously were classified as former smokers. Patients who had never smoked were classified as nonsmokers. The questionnaire was completed by 155 (87 per cent) of the 179 smokers.

HCS was measured throughout pregnancy by radioimmunoassay as previously described.[10] HCS values were obtained for 255 of the 271 women with normal pregnancy (770 determinations); median values and 95 per cent confidence limits are shown in Fig. 2 with curves of median values for abnormal patient groups superimposed upon the distribution of values of the normal population. For the 135 abnormal pregnancies, 302 HCS measurements were made on 128 girls.

Statistical methods. Statistical analysis of interview data pertaining to smoking characteristics was performed as published previously.[7] Comparisons of characteristics of smoking, nonsmoking, and formerly smoking patients were evaluated with the use of standard t statistics for comparisons of means. p Values (probabilities of a t statistic larger than the one observed if, in fact, the two populations had equal means) were computed for each comparison.

Statistical computations were performed on a computer* at the University of Kentucky Computing Center with the Statistical Package for Social Sciences.

Results

Demographic and obstetric findings. The adolescent clinic population is described in Fig. 1. In the 406 consecutive pregnancies studied, 271 (67 per cent) had a normal outcome and 135 (33 per cent) had an abnormal outcome by the criteria selected.[7] Racial differences were apparent in the abnormal pregnancies as noted in Table I. Although one third of the

*Model 360-65, IBM Corp., Data Processing Div., 112 E. Post Rd., White Plains, New York 10601

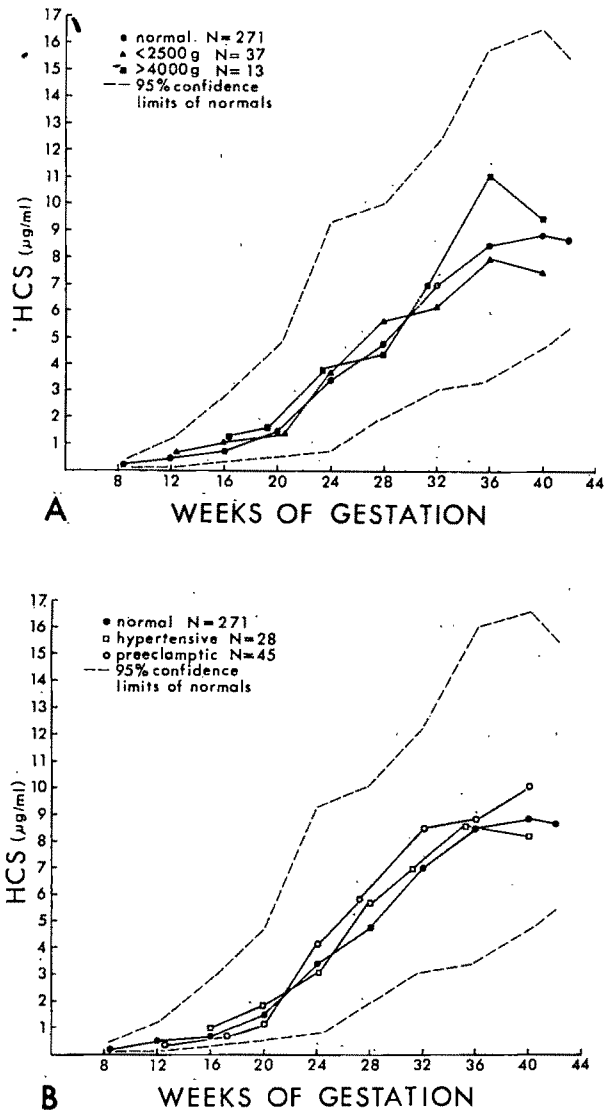


Fig. 2. HCS values throughout gestation in normal and abnormal adolescent pregnancies.

women in each race had abnormal pregnancies, the types of abnormalities differed in the two racial groups. There were significantly more babies <2,500 grams born to black mothers than to white mothers ($p < 0.05$), and significantly more babies of >4,000 grams were born to white mothers than to black mothers ($p < 0.01$). Black patients did not have a significantly higher spontaneous abortion or fetal loss rate than white patients.

Fig. 3. depicts the abnormal pregnancies in the total clinic population. Pre-eclampsia was the most common problem with pre-eclampsia and hypertension together accounting for 73 (54 per cent) of the 135 abnormal pregnancies.

Very few of the women in our study had adequate

Table I. Racial frequencies in normal and abnormal adolescent primiparous pregnancies

Study variable	*% Black (No. = 219)*	*% White (No. = 187)*
Normal	67 (147*)	66 (124)
Abnormal	33 (72†)	34 (63†)
Spontaneous abortion, Stillbirth, neonatal death	6 (12)	4 (8)
Infant <2,500 grams	12 (27‡)	5 (10)
Infant >4,000 grams	1 (2)	6 (11§)
Hypertension	8 (17)	6 (11)
Pre-eclampsia	9 (20)	13 (25)
Diabetes	0.5 (1)	0.5 (1)

*Number in parentheses is number of patients in study variable.

†Seven black and three white women had more than one abnormality.

‡By chi-square test, black women had significantly more babies <2,500 grams than white women ($p < 0.05$).

§By chi-square test, white patients had significantly more babies >4,000 grams than black patients ($p < 0.01$).

diets. Only 12 per cent of the total population had a diet grade of excellent or good; 46 per cent received a fair diet grade; and 42 per cent had a poor diet. There were no differences in diet grade between races or between the normal and abnormal populations. Similarly, anemia with an initial hematocrit of <35 per cent was found in 50 per cent of the women with normal pregnancies and 47 per cent of those with abnormal pregnancies (p = not significant). However, significantly more black women with abnormal pregnancies had anemia than white women with abnormal pregnancies (57 versus 35 per cent; $p < 0.05$).

Spontaneous abortion and fetal loss. Twenty women lost their infants. All lost infants were given equal weight statistically as they represent the same end result for the mother. In this adolescent group there were 12 spontaneous abortions, five neonatal deaths, and three stillbirths (Table II). Black patients did not have a significantly higher spontaneous abortion or fetal loss rate than white patients (6 versus 4 per cent).

The age at menarche was significantly younger in white women who aborted or lost their infants as compared to white women with normal pregnancies (11.0 versus 12.7 years; $p < 0.01$), but this was not a factor in the black group. Both racial groups had slightly lower prepregnancy weights than their control racial groups with normal pregnancies. Of the 14 smokers who aborted or lost their infants, none smoked more than 10 cigarettes per day. HCS levels of mothers who aborted or lost their infants were not different from those of mothers with normal pregnancies. These values were obtained early in pregnancy,

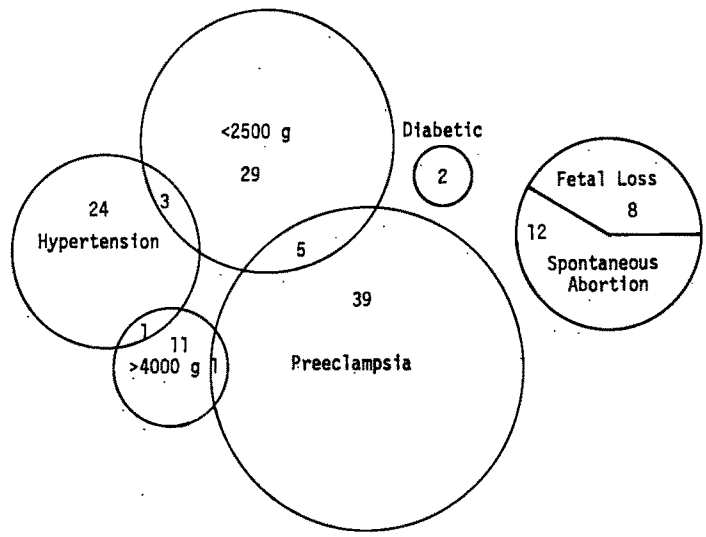


Fig. 3. Schematic distribution of abnormal adolescent pregnancies in women 12 to 18 years old.

Table II. Racial differences in adolescent primiparous women with spontaneous abortion or fetal loss (death)

Study variable	*Black*		*White*	
	Dead (No. = 12)	*Normal (No. = 147)*	*Dead (No. = 8)*	*Normal (No. = 124)*
Spontaneous abortion	(10*)		(2)	
Stillborn	(1)		(2)	
Neonatal death	(1)		(4)	
Smoker	(7)	(54)	(7)	(74)
Nonsmoker	(4)	(85)	(1)	(41)
Former smoker	(1)	(8)	(0)	(9)
Age at menarche (years)	12.1 (12)	12.3 (146)	11.0† (8)	12.7 (121)
Age at conception (years)	15.6 (12)	15.6 (147)	15.3 (8)	16.1 (124)
Prepregnancy weight (pounds)	118 (12)	128 (146)	114 (8)	122 (123)
Gestational age (weeks)	24‡ (5)	40 (144)	31† (6)	40 (120)

*Number in parentheses is number of patients in study variable.
†Significant difference between white dead and white normal babies ($p < 0.01$).
‡Significant difference between black dead and black normal babies ($p < 0.01$).

and no observations were available near the time of abortion.

Infants who weighed <2,500 grams at birth. There were 37 pregnancies (9 per cent) resulting in small infants (Table III). Black women had significantly more small babies than white patients (27 versus 10; $p < 0.05$). In women with small infants, there were no significant differences in age at menarche, age at conception, or prepregnancy weight compared with women with normal infants. Black mothers with small infants gained significantly less weight during pregnancy than black mothers with normal infants (19 versus 27 pounds; $p < 0.01$), and black small babies weighed less than white small babies (2,047 versus 2,280 grams; $p < 0.01$). Median HCS values of mothers with small infants (Fig. 2, *A*) fell within the normal range throughout gestation, but from the thirty-second week of gestation onward these mothers had the lowest median values of all patient groups. Placental weights were significantly decreased in both black and white patients ($p < 0.01$). In mothers who had small infants, there were 15 smokers, 19 nonsmokers, and three former smokers. Only one woman smoked more than 10 cigarettes per day.

Infants who weighed <4,000 grams at birth. There were 13 women who were delivered of infants >4,000 grams (Table III); white patients had significantly more large infants than black patients (11 versus 2; $p < 0.01$). Black women with large infants had excessive weight gain in pregnancy (44 versus 27 pounds; $p < 0.05$) and larger placentas (900 versus 619 grams; $p < 0.05$). Eleven white women had large infants. Their pregnancy weight gain was excessive (35 versus 28 pounds; $p < 0.05$), and the placentas were larger

Table III. Racial differences in adolescent primiparous women with infants <2,500 and >4,000 grams

Study variable	Black			White		
	<2,500 grams (No. = 27)	*Normal (No. = 147)*	*>4,000 grams (No. = 2)*	*<2,500 grams (No. = 10)*	*Normal (No. = 124)*	*>4,000 grams (No. = 11)*
Maternal						
Smoker	(8*)	(54)	(0)	(7)	(74)	(2)
Nonsmoker	(17)	(85)	(2)	(2)	(41)	(9)
Former smoker	(2)	(8)	(0)	(1)	(9)	(0)
Age at menarche (years)	12.4 (27)	12.3 (146)	12.0 (2)	11.9 (9)	12.7 (121)	12.8 (11)
Age at conception (years)	16.0 (27)	15.6 (147)	16.0 (2)	15.4 (10)	16.1 (124)	16.0 (11)
Prepregnancy weight (pounds)	123 (27)	128 (146)	114 (2)	110 (8)	122 (123)	123 (11)
Weight gain in pregnancy (pounds)	19 (27†)	27 (146)	44 (2‡)	20 (8)	28 (124)	35 (11§)
Placental weight (grams)	473 (24†)	619 (132)	900 (1‡)	471 (8‖)	629 (113)	826 (11‖)
Infant						
Weight (grams)	2,047 (27†¶)	3,152 (147)	4,185 (2†)	2,280 (10‖)	3,199 (124)	4,200 (11‖)
Length (cm.)	45 (23†)	49 (124)	54 (2‡)	46 (9‖)	50 (108)	54 (11‖)
Head circumference (cm.)	31 (25†)	34 (136)	37 (2†)	32 (10‖)	35 (119)	37 (11‖)
Gestational age (weeks)	36 (25†)	40 (144)	41 (2)	37 (10‖)	40 (120)	41 (10)

*Number is parentheses is number of patients in study variable.

†This measurement is significantly different from that of the normal black group ($p < 0.01$).

‡This measurement is significantly different from that of the normal black group ($p < 0.05$).

§This measurement is significantly different from that of the normal white group ($p < 0.05$).

‖This measurement is significantly different from that of the normal white group ($p < 0.01$).

¶The number of black infants <2,500 grams was significantly different from the number of white infants <2,500 grams ($p < 0.01$).

(826 versus 629 grams; $p < 0.01$) than those of white mothers with normal infants. Median HCS values for women with large infants (Fig. 2, *A*) showed a steep rise in the curve from 28 to 36 weeks' gestation. For this group, median HCS levels after 30 weeks' gestation were the highest of any of the abnormal groups.

Hypertension. There were 28 patients who had hypertension during pregnancy (17 black and 11 white, 7 per cent of the total study population). Unexpectedly, there was no difference in weight gain during pregnancy in either racial group compared to its normal control group or in black women with hypertension versus white women with hypertension (Table IV). There were significantly fewer smokers among hypertensive patients as compared with the number in the normal group ($p < 0.05$). Median HCS levels in hypertensive patients were slightly higher than normal from 26 to 36 weeks' gestation with a drift to lower than normal median levels after 36 weeks' gestation (Fig. 2, *B*).

Pre-eclampsia. There were 45 women with pre-eclampsia (20 black and 25 white women). White adolescents with pre-eclampsia (Table IV) gained significantly more weight during pregnancy than white normal patients (34 versus 28 pounds; $p < 0.05$) and had larger placentas (689 versus 629 grams; $p < 0.05$). Median HCS levels from 22 weeks' gestation onward were higher than those of normal and hypertensive patients, but the increase was not statistically significant (Fig. 2, *B*). The black pre-eclamptic women gained significantly less weight in pregnancy than the white pre-eclamptic patients (24 versus 34 pounds; $p < 0.05$). The infants of black pre-eclamptic mothers weighed significantly less (2,834 versus 3,316 grams; $p < 0.01$) than infants of white mothers with pre-eclampsia. Fifteen of 45 pre-eclamptic women were smokers, and of these only two smoked more than 10 cigarettes per day.

Diabetes mellitus. There were only two women in the study who had diabetes. One 14-year-old juvenile diabetic patient was delivered by cesarean section and had an infant with a patent ductus arteriosus. The second had gestational diabetes with an uneventful pregnancy and spontaneous delivery of a normal infant.

Comment

Demographic and obstetric data. This was a somewhat unusual prospective study as racial distribution of the study population was almost equal. Previous studies by Grant and Heald[5] have shown that population variables have made it difficult to interpret retrospective studies. Battaglia and colleagues[11] have shown that nonwhite women 14 years of age and younger from a low socioeconomic status are at high risk for complications of pregnancy. Israel and Woutersz[12] examined a large pool of data from a cooperative study of 10 hospitals in 1958. Although fetal loss was not

Table IV. Racial differences in adolescent primiparous women with hypertension and pre-eclampsia

Study variable	Black			White		
	Hypertensive (No. = 17)	*Normal (No. = 147)*	*Pre-eclamptic (No. = 20)*	*Hypertensive (No. = 11)*	*Normal (No. = 124)*	*Pre-eclamptic (No. = 25)*
Maternal						
Smoker	(2*)	(54)	(7)	(4)	(74)	(8)
Nonsmoker	(14)	(85)	(11)	(5)	(41)	(11)
Former smoker	(1)	(8)	(2)	(2)	(9)	(5)
Age at menarche (years)	11.7 (17)	12.3 (146)	12.5 (20)	12.2 (10)	12.7 (121)	12.1 (25†)
Age at conception (years)	15.6 (17)	15.6 (147)	15.6 (20)	16.2 (11)	16.1 (124)	15.9 (25)
Prepregnancy weight (pounds)	134 (17)	128 (146)	137 (19)	124 (11)	122 (123)	125 (25)
Weight gain in pregnancy (pounds)	25 (17)	27 (146)	24 (19)	28 (11)	28 (124)	34 (24†‡)
Placental Weight (grams)	607 (15)	619 (132)	628 (19)	652 (9)	629 (113)	689 (23†)
Infant						
Weight (grams)	3,151 (17)	3,152 (147)	2,834 (20§)	3,214 (11)	3,199 (124)	3,316 (25‖)
Length (cm.)	51 (16¶)	49 (124)	48 (18¶)	50 (7)	50 (108)	51 (21‖)
Head circumference (cm.)	35 (17)	34.3 (136)	33.7 (18¶)	35 (10)	34.6 (119)	34.8 (23‡)
Gestational age (weeks)	39 (17)	40 (144)	39 (19§)	40 (10)	39.9 (120)	40 (24‡)

*Number in parentheses is number of patients in study variable.

†This measurement is significantly different from that of the normal white group ($p < 0.05$).

‡This measurement is significantly different from that of the respective black group ($p < 0.05$).

§This measurement is significantly different from that of the normal black group ($p < 0.01$).

‖This measurement is significantly different from that of the respective black group ($p < 0.01$).

¶This measurement is significantly different from that of the normal black group ($p < 0.05$).

significantly different at <19 years of age, both white and nonwhite patients had more toxemia and prematurity than specific control subjects. Race (with lower black socioeconomic status) was a more important factor than age. Stine and co-workers,[13] Pakter and associates,[14] and Wiener and Milton[15] reached similar conclusions. Population selection is an extremely important factor as Semmens and Lamers[3] have shown in the virtual absence of excess complications of pregnancy in adolescence in a large armed service population with marital stability, an adequate socioeconomic status, the exclusion of the nonwhite race, and the availability of uniformly good medical care.

Racial comparisons in adolescent pregnancy. In our study of poor white and black patients, it was of interest that two thirds of the pregnancies in each racial group were normal. Prenatal care was uniform, and in normal pregnancies there were no significant racial differences in age at menarche, age at conception, prepregnancy weight, weight gain during pregnancy, placental weight, or infant measurements. The single distinguishing factor in the two racial groups with normal pregnancies was that only 37 per cent of the black group smoked compared with 60 per cent of the white group.

Racial differences were apparent in abnormal pregnancies. Black patients lost their infants significantly earlier than white patients (24 versus 31 weeks; $p < 0.01$). In the present study, the total fetal loss (fetal, neonatal, and perinatal deaths) of 4.0 per cent is slightly less than the 6.6 per cent figure calculated from the data of Israel and Woutersz[12] in women <19 years of age. Black women had small infants more than twice as often as white women ($p < 0.05$). This finding might be explained by the significantly shorter gestation period in these women (36 weeks). It was extremely unusual for a young black woman to have an infant who weighed >4,000 grams, and there were only two such instances in three years in contrast to eleven such infants of white mothers. It was interesting that these infants were not the products of women who were obese before pregnancy. In fact, the prepregnancy weight of those black mothers with large infants was less (not significantly) than that of the normal black control group. It may be extremely important that these women from 28 weeks' gestation onward produced more HCS than women who had small infants. The mothers with large infants gained significantly more weight and had significantly larger placentas than the normal control group. These results are compatible with the physiologic effect of increased placental growth hormone (HCS).

Hypertension was mild in this young population. Our findings of few smokers among pregnant women with hypertension are in agreement with the findings of Russell and associates,[16] Blackburn and colleagues,[17] Brown and co-workers,[18] and Kullander and Källen.[19]

In pre-eclampsia, white women had higher prepreg-

nancy, weights and gained more weight during pregnancy. These findings were coupled with slightly increased HCS median values and significantly larger placentas. The findings of shorter gestation periods and smaller infants in black women raise the possibility that pre-eclampsia may be more severe in nonwhite patients. Whether the hypertensive patients simply represented an earlier stage of pre-eclampsia cannot be established without precise etiologic criteria, but this seems a reasonable hypothesis. In this study there was not a single patient who went on to develop eclampsia, and there were no maternal deaths from any cause.

Smoking and adolescent pregnancy. The relationship of cigarette smoking to the outcome of pregnancy has been a confusing variable to analyze as noted by Yerushalmy[20] and Meyer and Comstock.[21] The initial difficulty stems from bias in selection of study cases and is further compounded by variable methods of data analysis. In the present study, by investigating first pregnancies in young black and white women of low economic status and examining pregnancy outcome in normal versus abnormal pregnancies by race, many selection biases were avoided.

It was surprising that in our 271 normal pregnancies there were more smokers (47 per cent) than in the 135 abnormal pregnancies (38 per cent). Mean birth weights of babies from white smokers with normal pregnancies were slightly but not significantly less than weights of babies of white nonsmokers with normal pregnancies (3,179 versus 3,239 grams). This was also true for infants of black smokers with normal pregnancies versus infants of black nonsmokers with normal pregnancies (3,104 versus 3,169 grams).

In women with abnormal pregnancies there were several interesting associations with smoking. Spontaneous abortion and fetal loss occurred in significantly more smokers than nonsmokers ($p < 0.01$), although the numbers were small. In mothers who had small infants (<2,500 grams), there were actually fewer smokers than nonsmokers. This may be an important observation as Yerushalmy[20] has noted that women who subsequently became smokers also had a high incidence of low–birth-weight infants during the period before they started to smoke. His evidence appeared to support the hypothesis that the higher incidence of low–birth-weight infants was due to the patient, not the smoking.

We were unable to find a relationship between smoking and development of hypertension or pre-eclampsia during pregnancy. There were fewer smokers than nonsmokers in these categories. We concluded that factors other than smoking must have greater etiologic significance in these diseases.

HCS in primiparous adolescent pregnancy. HCS has been shown to function in a physiologically similar way to both pituitary growth hormone and prolactin. Although HCS is synthesized by trophoblastic cells of the placenta, there is no understanding of possible mechanisms regulating its control and release. Spellacy and associates[7] have examined HCS values to evaluate placental function in managing high-risk pregnancies. They noted a decrease in HCS values in proportion to severity of maternal hypertension and determined a fetal danger zone (F-D zone = HCS values of <4 μg per milliliter after 30 weeks' gestation). In a later report,[23] it was found that values in the F-D zone occurred in only 1.4 per cent of normal pregnancies. In toxemia, HCS values were more frequently depressed with multiparity and severe hypertension (blood pressure > 160/110).

Ylikorkala[24] has studied 687 patients to determine the clinical importance of HCS as a fetoplacental function test in normal and complicated pregnancies. It was concluded that maternal age and HCS level were inversely related in pre-eclampsia but not in women with normal pregnancy. Mothers of infants with intrauterine growth retardation had significantly lower HCS levels than mothers with infants of normal weights ($p > 0.001$). HCS was believed to measure placental function effectively. A single subnormal HCS level during the third trimester of pregnancy was associated with fetal distress in 49 per cent of such pregnancies. More importantly, a single subnormal value and a decrease in HCS level in the same patient raised the risk of fetal distress to 69 per cent. These data and those of Spellacy and associates[23] and Lindberg and Nilsson[25] make a strong case for including HCS measurements in high-risk multiparous pregnancies, particularly in the third trimester.

Our findings in young primiparous patients are at variance with these, as somewhat higher than normal median HCS levels were noted in patients with mild pre-eclampsia from the twenty-second to fortieth weeks of gestation. Women who were delivered of small infants had lower than normal median HCS values after 30 weeks' gestation. Women who were delivered of large infants had higher than normal HCS levels after 32 weeks' gestation. In 19 observations (18 patients) of HCS in the F-D zone, we did not have a single fetal death. Moreover, in the present study, values in the F-D zone occurred in 4.4 per cent (12 patients) of normal pregnancies. No subsequent explanation for the low HCS values was apparent. In abnormal pregnancies, we found exactly the same percentage (4.4 per cent) of values in the F-D zone (six patients). Five of these women subsequently had living

infants <2,500 grams, and one patient was hypertensive but had a normal infant. In our study of very young primiparous women, HCS values were not helpful in predicting the outcome of pregnancy.

The authors wish to thank Drs. Harlley McKean, Keary Bemis, Grant Somes, and G. D. Gupta from the Departments of Statistics and Community Medicine for statistical consultation.

REFERENCES

1. Oppel, W. C., and Toyston, A. B.: Am. J. Public Health **61:** 751, 1971.
2. Osofsky, H. J., and Osofsky, J. D.: Am. J. Orthopsychiatry **40:** 825, 1970.
3. Semmens, J. P., and Lamers, W. M.: Teenage Pregnancy, Springfield, Illinois, 1968, Charles C Thomas, Publisher.
4. Osofsky, H.: The Pregnant Teenager: A Medical, Educational, and Social Analysis, Springfield, Illinois, 1968, Charles C Thomas, Publisher.
5. Grant, J. A., and Heald, F. P.: Clin. Pediatr. **11:** 567, 1972.
6. Moser, R. J., Hollingsworth, D. R., Carlson, J. W., and Lamotte, L.: AM. J. OBSTET. GYNECOL. **120:** 1080, 1974.
7. Spellacy, W. N., Teoh, E. S., Buhi, W. C., Birk, S. A., and McCreary, S. A.: AM. J. OBSTET. GYNECOL. **109:** 588, 1971.
8. Hellman, L. M., and Pritchard, J. A.: Williams' Obstetrics, ed. 14, 1971, New York, Appleton-Century-Crofts, Inc., pp. 685-689.
9. Moody, P. M., Averitt, J. H., and Griffith, R. B.: Proceedings of the University of Kentucky Tobacco and Health Research Institute, Lexington, March, 1973, p. 18.
10. Moser, R. J., and Hollingsworth, D. R.: Clin. Chem. **19:** 602, 1973.
11. Battaglia, F. C., Frazier, T. M., and Hellegers, A. E.: Pediatrics **32:** 902, 1963.
12. Israel, S. L., and Woutersz, T. B.: AM. J. OBSTET. GYNECOL. **85:** 659, 1963.
13. Stine, O. C., Rider, R. V., and Sweeney, E.: Am. J. Public Health **54:** 1, 1964.
14. Pakter, J., Rosner, H. J., Jacobziner, H., and Greenstein, F.: Am. J. Public Health **51:** 846, 1961.
15. Wiener, G., and Milton, T.: Am. J. Epidemiol. **91:** 260, 1970.
16. Russell, C. S., Taylor, R., and Law, C. E.: Br. J. Prev. Soc. Med. **22:** 119, 1968.
17. Blackburn, H., Brozek, J., Taylor, L., and Keys, A.: Ann. N. Y. Acad. Sci. **90:** 277, 1960.
18. Brown, R. G., McKeown, T., and Whitfield, A. G. W.: Br. J. Prev. Soc. Med. **11:** 162, 1957.
19. Kullander, S., Källen, B.: Acta Obstet. Gynecol. Scand. **50:** 83, 1971.
20. Yerushalmy, J.: AM. J. OBSTET. GYNECOL. **112:** 277, 1972.
21. Meyer, M. B., and Comstock, G. W.: Am. J. Epidemiol. **96:** 1, 1972.
22. Kaplan, S. L., and Grumbach, M. M.: J. Clin. Endocrinol. Metab. **24:** 80, 1964.
23. Spellacy, W. N., Buhi, W. C., Birk, S. A., and McCreary, S. A.: AM. J. OBSTET. GYNECOL. **120:** 214, 1974.
24. Ylikorkala, O.: Acta Obstet. Gynecol. Scand. **26:** 1, 1973. (Suppl.)
25. Lindberg, S., and Nilsson, A.: J. Obstet. Gynaecol. Br. Commonw. **80:** 1046, 1973.

Measurement of the pre-ejection period during labor with the use of arterial pulse time

A. BERNSTEIN, M.D.
L. W. ORGAN, M.D., B.A.Sc.
L. E. EISNER, M.A.Sc.
K. C. SMITH, PH.D.
I. H. ROWE, PH.D.
Toronto, Ontario, Canada

A new fetal parameter, the arterial pulse time, is described. It is the time from the onset of the fetal electrocardiographic recording to the arrival of the arterial pulse wave recorded at the fetal head. Since arterial pulse time differs from the pre-ejection period by only an apparently constant value, it is proposed as a potential method for obtaining the pre-ejection period during labor.

THE ABILITY TO DETECT significant changes in fetal status during labor has improved over the past several years with the use of continuous heart rate monitoring and scalp capillary blood sampling for pH and blood gases. Both techniques have limitations. Heart rate patterns cannot always unequivocally indicate the presence or absence of fetal distress, and scalp sampling is technically too cumbersome. In previous work we have shown that a new fetal parameter, the pre-ejection period (PEP), can be measured during labor.[1] PEP is defined as the time from the beginning of the QRS complex of the electrocardiogram to the onset of ejection of blood from the left ventricle, i.e., aortic valve opening (Fig. 1). Experiments in stressed fetal lambs showed that PEP reflects changes in umbilical blood flow and fetal Po_2 in a reliable, consistent manner.[2] These changes are thought to be produced by effects on the inotropic state and loading of the fetal heart as previously reported and illustrated in Fig. 2.

Determination of PEP requires the fetal electrocardiogram and some indicator of the time of the aortic valve opening. There is no technologic problem in obtaining the fetal electrocardiogram—the scalp clip electrode technique has been used successfully for many years. The entire problem is that of detecting aortic valve opening. This report describes our progress in a new technique with the use of arterial pulse wave detection for measurement of PEP.

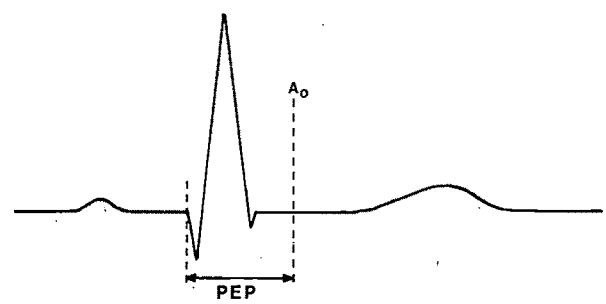


Fig. 1. The PEP of the cardiac cycle. A_o, aortic valve opening.

Method

Ejection of blood into major vessels during the systolic phase of the heart cycle produces a peripheral arterial pulse distributed throughout the body. The arrival time of the pulse at any given point in the periphery depends on distance from the heart and elasticity of the arterial tree. In addition, systolic heart movement, as, for example, during isovolumetric contraction, and subsequent blood ejection are associated with reaction forces which produce instantaneous minute whole-body movements, especially in the direction of the long-body axis. Detecting and recording these reaction movements constitutes the ballistocar-

From the Departments of Obstetrics and Gynecology, Physiology, and Electrical Engineering, University of Toronto, and the Mount Sinai Hospital.

Received for publication August 5, 1975.

Revised October 21, 1975.

Accepted November 14, 1975.

Reprint requests: Dr. A. Bernstein, Department of Obstetrics and Gynecology, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario, M5G 1X5, Canada.

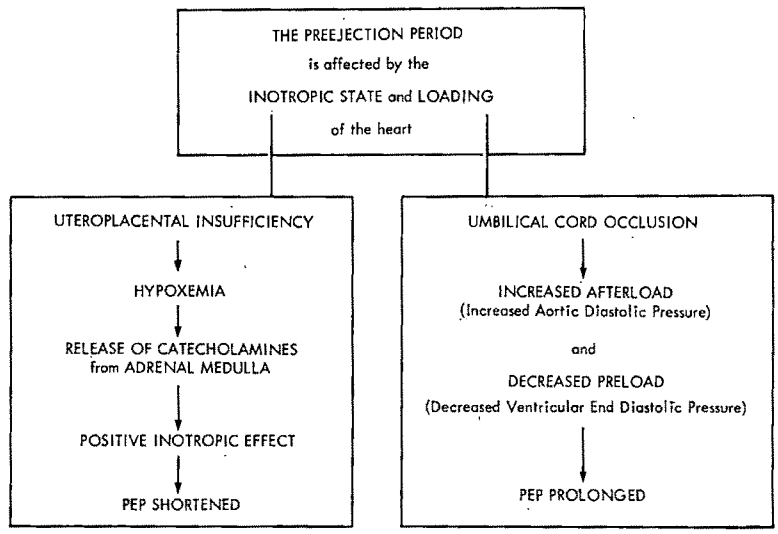


Fig. 2. Proposed mechanisms of PEP change during fetal stress.

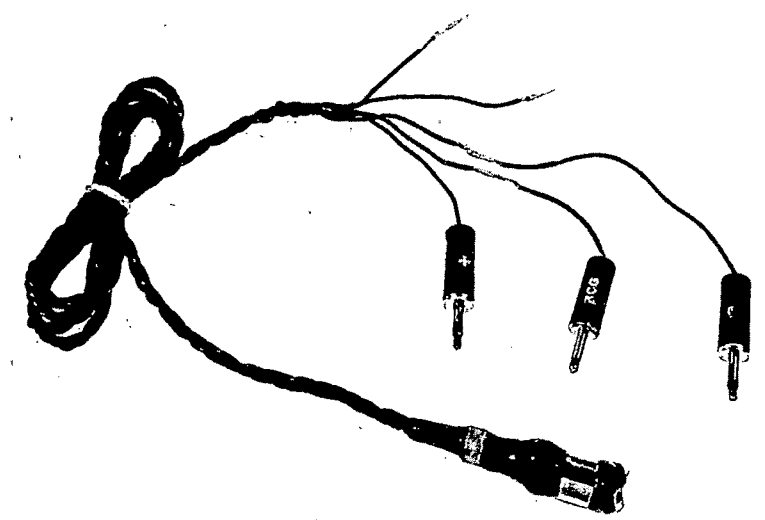


Fig. 3. The combined sensor for attachment to the fetal scalp to record both body movements and the electrocardiogram.

diogram. Since both the arterial pulse wave and the ballistocardiogram are associated with systolic ejection, a technique that records movements produced by one or both of these sources will contain a wave form related to aortic valve opening.

The movement sensor used in this study was a miniature compression-type piezoelectric accelerometer.* The accelerometer and a preamplifier were encapsulated in an aluminum cylinder 30 mm. long and 14 mm. in diameter. Three slightly curved, sharpened, stainless steel wires were mounted around the circumference of one end of the cylinder to form a spiral electrode configuration (Fig. 3). This served the dual purpose of providing a means of connecting the device to the fetal scalp and, as well, a source of the fetal electrocardiogram. Eleven patients in normal labor at Mount Sinai Hospital, Toronto, were used in this study. The protocol consisted of insertion of an intra-amniotic catheter, followed by connection of the combined accelerometer/electrode to the fetal scalp at a site not over a fontanelle. Fetal heart rate and uterine contractions were displayed on a standard fetal monitor, while the acceleration data, fetal electrocardiogram, and intra-amniotic fluid pressure were stored on magnetic tape in a tape recorder* operated in the

*No. 8303, Bruel & Kjaer.

*Model PI-6200, Precision Data, Inc., Mountain View, California.

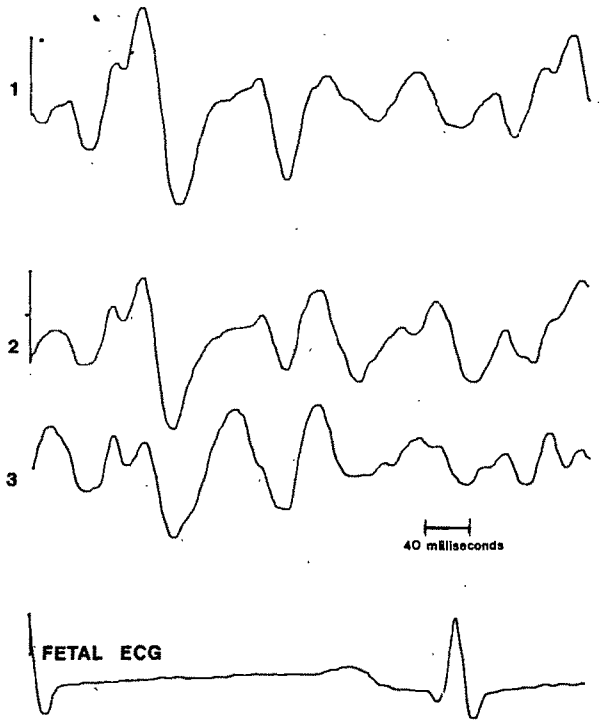


Fig. 4. Three consecutive acceleration arterial pulse waves recorded at the fetal head. Each is an average of eight individual pulse waves. The simultaneously recorded fetal electrocardiogram is used as a time reference.

FM mode with band pass DC to 1 kHz. In three patients, Doppler ultrasound recordings of aortic valve movement were also obtained and stored.

The accelerometer signal was electronically averaged on a Signal Analyzer System* over eight consecutive heartbeats to enhance the signal-to-noise ratio. Eight was chosen empirically from the observation that, as a rule, signal clarity improved up to about this number and tended to "average out" beyond it due to trend variations in wave-form latency. The resultant waveform is called an arterial pulse wave. This wave form is a record of acceleratory movements because of the nature of the transducer and, therefore, is more rigorously termed the "acceleration arterial pulse wave." It was observed that its derivative, the jerk arterial pulse wave, contained more easily identifiable peaks when comparing results from different subjects. The jerk arterial pulse wave was obtained by first passing the accelerometer signal through a differentiator linear to 1 kHz. and then averaging eight heart cycles as above.

*Model 5480B, Hewlett-Packard Co., San Diego Div., San Diego, California.

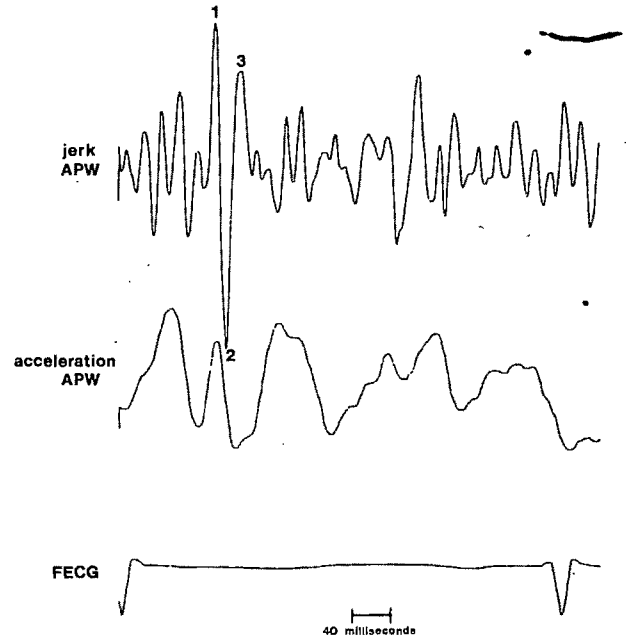


Fig. 5. The effect of differentiating the acceleration arterial pulse wave *(APW)* to obtain the jerk *APW*.

Results

Three acceleration arterial pulse waves, obtained consecutively in the same fetus, are shown in Fig. 4. The averaged fetal electrocardiogram is shown at the bottom of the figure. Fig. 5 is a record of the jerk arterial pulse wave and the acceleration pulse wave from which it was obtained. Use of any one of the relatively sharp peaks—1, 2, or 3—of the jerk arterial pulse wave allows easy determination of arterial pulse time by measuring along the time axis from the fetal electrocardiogram to a chosen peak. We used Peak 3 in this study. Arterial pulse time was measured manually from the averaged data (jerk arterial pulse wave and fetal electrocardiogram) stored on the oscilloscope screen of the Signal Analyzer. One measurement of arterial pulse time was determined for about every 10 seconds of labor. Records of arterial pulse times, together with fetal heart rate and uterine contractions, are shown in Figs. 6 and 7, with patterns suggestive of those seen experimentally in the fetal lamb and clinically in the human fetus with Doppler ultrasound used for PEP determination.[3] Most results were not technically as good as the ones shown, and computation was laborious, but feasibility is demonstrated.

Comment

The initial objective of our research was to obtain the fetal ballistocardiogram by attaching an accelerometer



Fig. 6. An arterial pulse time "pattern." Absolute values for arterial pulse time are not indicated because of the arbitrary nature of the choice of reference points for its determination.

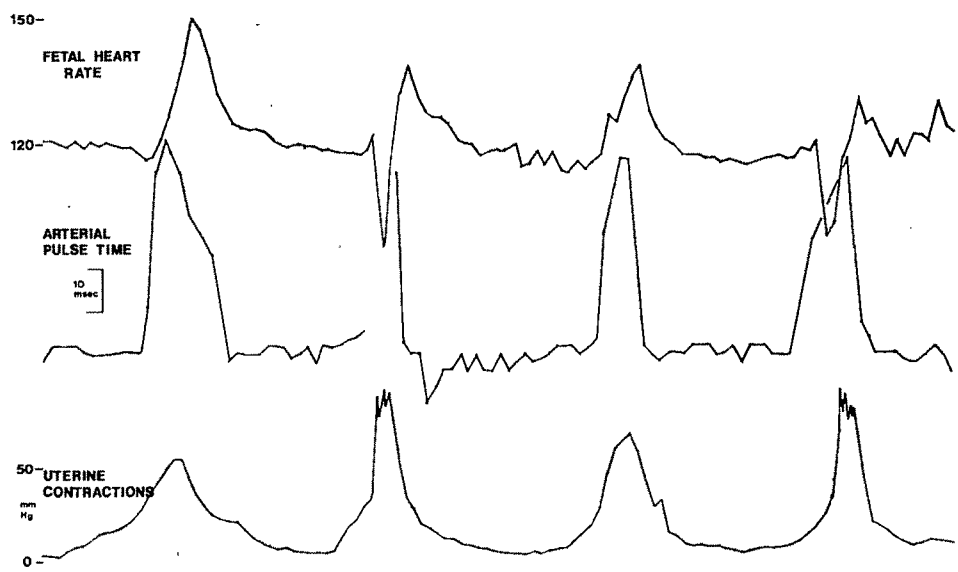


Fig. 7. An arterial pulse time "pattern."

transducer to the fetal head. The fetal ballistocardiogram has been obtained by Curran and associates[4] from signals produced by the movement of a frictionless, air-bearing bed supporting the pregnant woman near term. The maternal ballistrocardiogram is, of course, also available. This traditional method of obtaining a ballistocardiogram is not suitable for the labor room environment because the ballistocardiographic bed is essentially an unyielding weighted slab on rails and because of the requirement for the mother to remain motionless. To substantiate whether or not the movement recorded at the fetal head by the accelerometer was, in fact, a ballistocardiogram, simultaneous records were obtained of the accelerometer output, the fetal electrocardiogram, and the aortic valve opening obtained by Doppler ultrasound. Fig. 8 illustrates the results. The processed accelerometer output—the jerk response—occurs after aortic valve opening. This implies that it is produced by an arterial pulse wave arriving at the fetal head and not by the ballistocardiogram because a ballistocardiogram wave form would have started before aortic valve opening since it contains components related to isovolumetric contraction.

This finding was further substantiated by an exper-

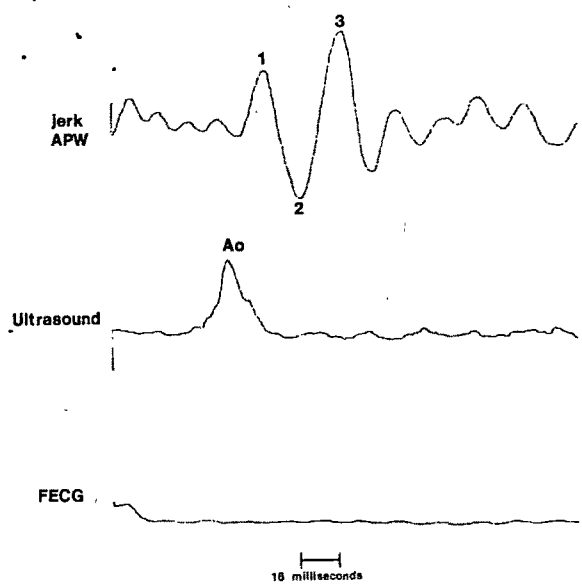


Fig. 8. Simultaneously recorded jerk arterial pulse wave *(APW)*, Doppler ultrasound for aortic vlave opening *(Ao)*, and fetal electrocardiogram.

iment on an adult subject where the combined accelerometer/electrode was taped first over the carotid artery and then on the vertex, and the results were compared. The electrocardiogram, obtained in a conventional manner, was recorded to serve as a timing reference. The wave form produced by the combined device mounted on the lateral aspect of the neck over the carotid artery would result primarily from carotid artery movement with relatively little from the ballistocardiogram because the accelerometer was perpendicular to the long axis of the body, which is the main direction of ballistocardiographic movement. The accelerometer, when mounted on the vertex, was oriented in the direction of the long-body axis to allow a significant ballistocardiogram component, if present, to be recorded. The results, in Fig. 9, show a longer latency of the wave form at the vertex than at the

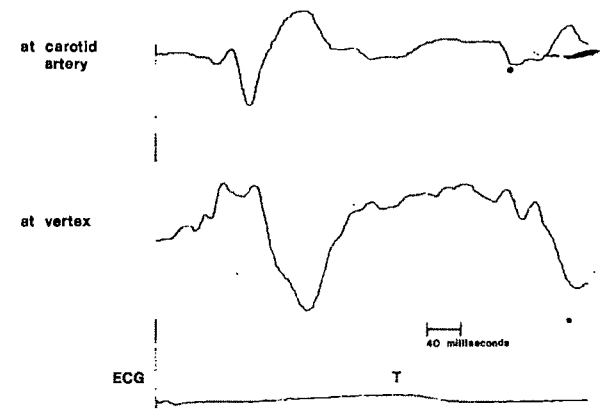


Fig. 9. The arrival time of the acceleration arterial pulse wave at the carotid artery and at the vertex of an adult subject.

carotid artery—further evidence that an arterial pulse rather than the ballistocardiogram is recorded at the vertex.

Arterial pulse wave velocity is dependent upon arterial distensibility, becoming faster with decreasing distensibility. Therefore, arterial pulse time is subject to an influence not necessarily related to the PEP. However, variation in arterial distensibility between fetuses is almost certainly insignificant. It is likely, then, that arterial pulse time differs from PEP only by a segment of time which appears to be constant and, therefore, could be useful as an indicator of the PEP because changes, rather than absolute values, are most significant. Since the arterial pulse "shock wave" rather than the acceleratory whole-body movements is the phenomenon measured, other transducers, sensitive to displacement or velocity, could be used in an attempt to increase sensitivity and decrease size.

The authors would like to acknowledge Miss Hazel Aurora Meghu for the nursing care provided and subsequent assistance at the laborious process of analyzing results.

REFERENCES

1. Organ, L. W., Bernstein, A., Rowe, I. H., and Smith, K. C.: Am. J. Obstet. Gynecol. **115:** 369, 1973.
2. Organ, L. W., Milligan, J. E., Goodwin, J. W., and Bain, M. J. C.: Am. J. Obstet. Gynecol. **115:** 377, 1973.
3. Organ, L. W., Bernstein, A., Smith, K. C., and Rowe, I. H.: Am. J. Obstet. Gynecol. **120:** 49, 1974.
4. Curran, J. T., Kerr, J., and MacGregor, J.: Proc. 2nd. World Congr. Ballistocard. Cardiovasc. Dynamics. Oporto, 1969, Bibl. Cardiol **26:** 230, 1970.

Observations on maternal oxytocin release during human labor and the effect of intravenous alcohol administration

G. L. D. GIBBENS, M.R.C.O.G.

T. CHARD, M.D., M.R.C.O.G.

London, England

Serial blood samples were obtained from 97 women in spontaneous labor, and oxytocin levels were determined by a sensitive and highly specific radioimmunoassay. The following observations were made: (1) The hormone is released in a series of "spurts"; (2) the peak levels achieved are usually 2 to 5 μU per milliliter and never exceed 12.5 μU per milliliter; (3) the frequency of spurt release increases as labor progresses, reaching a maximum in the second stage; (4) the frequency of spurt release is reduced during intravenous infusion of alcohol at levels which produce no obvious effect on uterine activity.

MANY FACTORS CAN influence the contractility of the human uterus at term. One of the best known of these is oxytocin, but the role that it plays in spontaneous human parturition is uncertain.[1, 2] Direct estimation of oxytocin in the maternal circulation has yielded conflicting results[3–16] (Table I), and there is also evidence for release by the fetal pituitary.[12, 16, 17] In the present studies, circulating oxytocin levels in serial samples from women during unstimulated labor have been examined by means of a highly specific and sensitive radioimmunoassay. In addition, the effects of intravenous administration of alcohol have been investigated.

Subjects and methods

Eight serial samples were collected from each of 57 patients during spontaneous labor (first stage, 33 subjects; second stage, 14 subjects; third stage, 10 subjects). Single samples were also taken from a further 30 subjects during the third stage. The serial samples were collected over a period of 4 to 8 minutes, and the timing of each sample in relation to manually palpated uterine contractions was noted. For analysis of results, the first stage was divided into four equal time periods. An additional set of serial samples was taken from 10 patients in established spontaneous labor (cervical dilation, 6 cm. or greater) having received an infusion of 10 per cent alcohol in 5 per cent dextrose (12.5 ml. per hour per kilogram of body weight for one hour). All patients in this group were in Phase 3 or 4 of the first stage or the early second stage. All samples were collected in cooled syringes containing heparin and immediately separated at 4° C.; plasma (5 ml.) was acidified to pH 1 to 2 before storage at −20° C. until assay. Plasma levels of oxytocin were measured by radioimmunoassay,[11] with synthetic oxytocin* used for standard and radioiodination and glass beads† used for extraction. All extracts were assayed by four serial dilutions in assay buffer. The minimum detection limit of this assay is 1.5 pg. (0.75 μU) per milliliter of plasma. Addition of ethanol to the blood samples has no effect on the recovery of exogenous or endogenous hormone.

From the Department of Human Reproduction and Obstetrics, University of Southampton, and the Departments of Obstetrics and Gynaecology and of Reproductive Physiology, St. Bartholomew's Hospital Medical College.

Financial support was provided by the Medical Research Council, The Spastics Society, and the Board of Governors of St. Bartholomew's Hospital.

Received for publication August 6, 1975.

Accepted December 9, 1975.

Reprint requests: Dr. T. Chard, St. Bartholomew's Hospital Department of Reproductive Physiology, 51-53 Bartholomew Close, London, E.C.1, England.

*Syntocinon, Sandoz Pharmaceuticals, Div. of Sandoz-Wander, Inc., Route 10, Hanover, New Jersey 07936.

†Spherosil XOA 400.

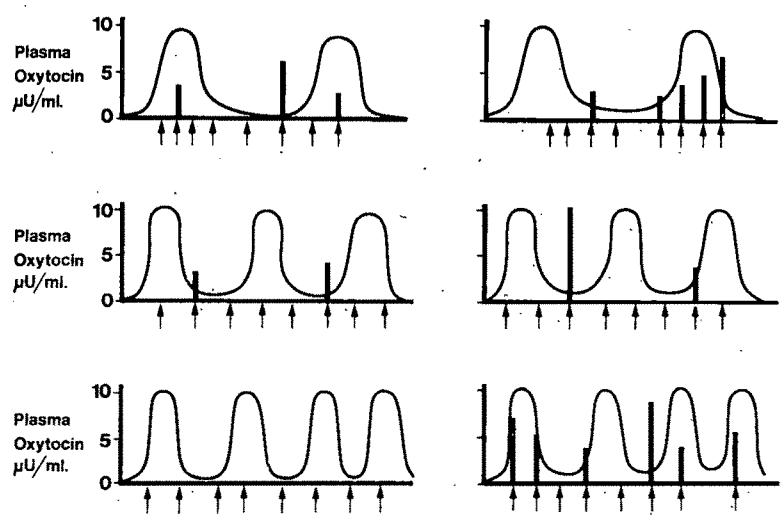


Fig. 1. Serial plasma oxytocin levels in six subjects in normal spontaneous labor, superimposed on the pattern of uterine contractions (continuous line). The time of sample collection is shown by arrows, and the oxytocin level is shown by vertical bars. Where no vertical bar appears, the sample contained no oxytocin detectable by radioimmunoassay.

Table I. Levels of oxytocin in the maternal circulation found in various series

Assay	*Extraction procedure*	*Oxytocin levels (μU/ml.)*		*Series*
		First stage	*Second stage*	
Bioassay	—		140	Fitzpatrick[3] (1961)
Bioassay	Acetone-ether	1,390		Hawker and associates[4] (1961)
Bioassay	—	30,000-50,000		Juret and colleagues[5] (1961)
Bioassay	—	20-40	2,000-4,000	Coutinho[6] (1964)
Bioassay	—		300-900	Coch and co-workers[7] (1965)
Bioassay	Sephadex		80-200	Fitzpatrick and Walmsley[8] (1965)
Immunoassay	Sephadex		7,500	Bashore[9] (1967)
Immunoassay	Acetone-ether	10-75	100-200	Glick and associates[10] (1969)
Immunoassay	Fuller's earth	0	0	Chard and colleagues[11] (1970)
Immunoassay	Fuller's earth	0-18		Chard and co-workers[12] (1971)
Immunoassay	Fuller's earth	0-12.5		Gibbens and associates[13] (1972)
Bioassay	—	0	0	Vorherr[14] (1973)
Immunoassay	—	35-435		Kumaresan and colleagues[15] (1974)
Immunoassay	—		82-90	Kumaresan and co-workers[16] (1975)

Results

In many samples no oxytocin could be detected (less than 0.75 μU per milliliter). Positive levels occurred intermittently; typical patterns from six subjects are shown in Fig. 1 and are characteristic of "spurt" release. A progressive increase in the number of positive results was apparent throughout the first stage, reaching a maximum (64 per cent) in the second stage and falling in the third stage (Table II and Fig. 2). The majority of positive results were between 2 and 5 μU per milliliter, and the levels never exceeded 12.5 μU per milliliter. There was no obvious relationship between positive results and the occurrence of uterine contractions, and the frequency of "spurts" was unrelated to the degree and timing of sedation. During alcohol infusion, the frequency of positive results was

considerably reduced when compared with that in untreated subjects at a comparable stage of labor (Fig. 2). There was no effect on the frequency or amplitude of contractions.

Comment

The findings reported here go some way toward resolving an earlier dispute on the exact nature of maternal oxytocin release during spontaneous human labor. With one exception,[14] previous investigators using direct assays have reported exceptionally high levels which are incompatible with indirect evidence: In other words, the levels observed were of orders of magnitude greater than those which can be calculated from the rates of infusion required to induce contractions in the uterus at term.[1, 18–21] In the case of bioassays, the high values can be attributed to the presence in blood of materials which mimic the effect of oxytocin or to the use of jugular venous plasma[7]; in the case of radioimmunoassays, it can be attributed to the failure to use an extraction procedure or to take adequate precautions to obviate proteolytic destruction of the tracer hormone.[2] The present results also differ somewhat from our own previous findings[11, 12] inasmuch as the incidence of positive values is much increased. This can be attributed to two factors: (1) The earlier studies were based largely on isolated rather than serial samples (the latter provide within-patient control for "positive" versus "negative" findings); (2) glass beads rather than Fuller's earth were used for extraction, which together with the assay of serial dilutions of each extract yields a considerable increase in precision and, thus, of confidence statistically in the distinction of positive and negative values.

The present results show levels which are compatible with the indirect evidence, and the specificity of the findings is further confirmed by the observation of inhibition of oxytocin release associated with intravenous ethanol. Furthermore, the pattern of "spurt" release of hormone is similar to that seen in animals during suckling[22] and sexual activity[23] and in the human subject during prostaglandin infusion.[24] This type of release would seem to be characteristic of oxytocin and is closely reflected by the electrical activity of the neurons of the hypothalamic paraventricular nucleus.[25] Given a pattern of "spurt" release, there are considerable problems in estimating the total amount of hormone released in spontaneous labor. Simple integration of the results (frequency × amplitude) will probably yield a false picture, since the distribution and clearance of the hormone will be very different when it is delivered to the circulation as a series of "spurts" from that when it is delivered continuously. Earlier

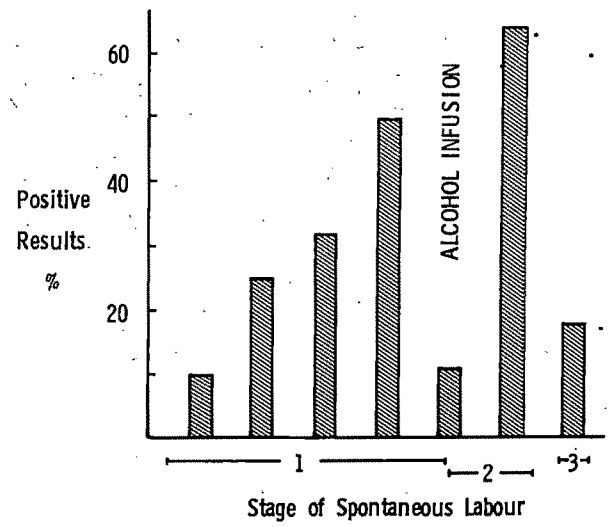


Fig. 2. Per cent of positive results related to stage of labor.

Table II. The incidence of positive results (oxytocin levels greater than 0.75 μU per milliliter) in serial samples from women during spontaneous labor

Stage	*No. of subjects*	*No. of samples*	*Samples with positive results*	
			No.	*%*
First				
1	6	48	5	10
2	9	72	18	25
3	12	96	31	33
4	6	48	24	50
Second	14	112	72	64
Third	40	110	16	15
Alcohol infusion	10	80	9	11

results[26] with the use of the same assay on maternal urine suggest that the effective rate is unlikely to exceed 1 mU. per minute.

The functional significance of the present observations is uncertain. Most of the increase in oxytocin release is associated with the process of labor and, therefore, could be a secondary rather than a primary phenomenon. There was no obvious relationship between individual "spurts" and uterine contractions, although the effect of sporadic release could be "smoothed" at the target organ by binding to high-affinity receptor sites.[27] However, the fact that inhibition of oxytocin release by ethanol administration was not associated with any effect on uterine contractions in advanced labor suggests that, at this stage, oxytocin is not a sine qua non for myometrial activity.

Finally, these results provide the first direct, as opposed to indirect, evidence that ethanol can inhibit

release of oxytocin from the posterior pituitary. In earlier studies[28–30] it has been difficult to exclude completely the possibility that the effect of ethanol was on the target organ. In the present studies, there was no effect on target organ response; therefore, the only possible explanation for the striking fall in oxytocin release is via a direct effect on the posterior pituitary gland.

We are grateful to the consultant staff of St. Bartholomew's Hospital and Southampton General Hospital for permission to study their patients and to Mrs. Stella Hollingsworth for her help with the assay.

REFERENCES

1. Theobald, G. W.: Obstet. Gynecol. Survey **23:** 109, 1968.
2. Chard, T.: Mem. Soc. Endocrinol. **20:** 61, 1973.
3. Fitzpatrick, R. J.: J. Endocrinol. **22:** xix, 1961.
4. Hawker, R. W., Walmsley, C. F., Roberts, V. S., Blackshaw, J. K., and Downs, J. C.: J. Clin. Endocrinol. **21:** 985, 1961.
5. Juret, T., Suzor, R., and Poli Marchetti, P.: Quoted by Driessche, R. V., *in* Caldeyro-Barcia, R., and Heller, H., editors: Oxytocin, New York, 1961, Pergamon Press, Inc., p. 400.
6. Coutinho, E. M.: Second International Congress of Endocrinology, Amsterdam, 1964, Excerpta Medica Foundation, International Congress Series 64.
7. Coch, J. A., Brovetto, J., Cabot, H. M., Fielitz, C. A., and Caldeyro-Barcia, R.: AM. J. OBSTET. GYNECOL. **91:** 10, 1965.
8. Fitzpatrick, R. J., and Walmsley, C. R.: *In* Pinkerton, J. H. M., editor: Advances in Oxytocin Research, London, 1965, Pergamon Press, Inc., p. 51.
9. Bashore, R. A.: Obstet. Gynecol. **29:** 431, 1967.
10. Glick, S. M., Kumaresan, P., Kagen, A., and Wheeler, M.: *In* Margoulies, M., editor: Protein and Polypeptide Hormones, Amsterdam, 1969, Excerpta Medica Foundation, p. 81.
11. Chard, T., Boyd, N. R. H., Forsling, M. L., McNeilly, A. S., and Landon, J.: J. Endocrinol **48:** 223, 1970.
12. Chard, T., Hudson, C. N., Edwards, C. R. W., and Boyd., N. R. H.: Nature **234:** 352, 1971.
13. Gibbens, D., Boyd, N. R. H., and Chard, T.: J. Endocrinol. **53:** liv, 1972.
14. Vorherr, H.: *In* Assali, N. S., editor: Pathophysiology of Gestation, New York, 1972, vol. 1, Academic Press, Inc., p. 145.
15. Kumaresan, P., Anandarangam, P. B., Dianzon, W., and Vasicka, A.: AM. J. OBSTET. GYNECOL. **119:** 215, 1974.
16. Kumaresan, P., Han, G. S., Anandarangam, P. B., and Vasicka, A.: Obstet. Gynecol. In press.
17. Seppälä, M., Aho, I., Tissari, A., and Ruoslahti, E.: AM. J. OBSTET. GYNECOL. **114:** 788, 1972.
18. Caldeyro-Barcia, R., and Poseiro, J. J.: Ann. N. Y. Acad. Sci. **78:** 813, 1959.
19. Gonzalez-Panizza, V. H., Sica-Blanco, Y., and Mendez-Bauer, C.: *In* Caldeyro-Barcia, R., and Heller, H., editors: Oxytocin, New York, 1961, Pergamon Press, Inc., p. 347.
20. Saameli, K.: AM. J. OBSTET. GYNECOL. **85:** 185, 1963.
21. Mantell, C. D., and Liggins, G. C.: J. Obstet. Gynaecol. Br. Commonw. **77:** 976, 1970.
22. McNeilly, A. S.: J. Endocrinol. **52:** 177, 1927.
23. McNeilly, A. S., and Drucker, H. A.: J. Endocrinol. **54:** 399, 1972.
24. Gillespie, A., Brummer, H. C., and Chard, T.: Br. Med. J. **1:** 543, 1972.
25. Wakerley, J. B., and Lincoln, D. W.: J. Endocrinol. **57:** 477, 1973.
26. Boyd, N. R. H., and Chard, T.: AM. J. OBSTET. GYNECOL. **115:** 827, 1973.
27. Soloff, M. S., and Swartz, T. L. J. Biol. Chem. **248:** 6471, 1973.
28. Wilson, K. H., Landesman, R., Fuchs, A.-R., and Fuchs, F.: AM. J. OBSTET. GYNECOL. **104:** 436, 1969.
29. Gimeno, M. A. R., Bedners, A. S., de Vastik, F. J., and Gimeno, A. L.: Arch. Int. Parmacodyn. Ther. **191:** 213, 1971.
30. Fuchs, F., Fuchs, A.-R., Poblete, V., and Rizk, A.: AM. J. OBSTET. GYNECOL. **112:** 610, 1972.



Ortho-Novum 1/80 □ 21

Each tablet contains 1 mg norethindrone and 0.08 mg mestranol. TRADEMARK

a history of good patient acceptance

low incidence of breakthrough bleeding

Less than 2% overall experience in 3,464 women over 34,068 cycles.

low incidence of spotting

Less than 3% overall experience in 3,464 women over 34,068 cycles.

low dropout rate

Only 3.6% of women in clinical studies dropped out because of adverse reactions. Serious as well as minor conditions have been reported following the use of oral contraceptives. These conditions include thromboembolic disease. The physician should remain alert to the earliest manifestation of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

highly effective

Ortho-Novum 1/80 □ 21 is a highly effective, well-balanced oral contraceptive. Moreover, it is packaged in the unique crush-proof DIALPAK* Tablet Dispenser to help reduce the chance of patient failure. Also available in a 28-day DIALPAK Tablet Dispenser.

See prescribing information on following page.

*TRADEMARK © OPC 1975

Ortho-Novum 1/80 21 and 28

TRADEMARK

Each white tablet contains 1 mg norethindrone and 0.08 mg mestranol.
Each green tablet in the 28-day regimen contains inert ingredients.

a history of good patient acceptance



Ortho-Novum 1/80□21 and Ortho-Novum 1/80□28

Description: Each white ORTHO-NOVUM 1/80 tablet contains 1 mg of the progestational substance, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol. Each green tablet in the 28-day regimen contains inert ingredients.

Actions: ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of or contraceptives.

Precautions: 1. A thorough history and physical examination should be performed befo prescribing oral contraceptives and periodically during their administration and shou include special reference to breasts and pelvic organs, including Papanicolaou smear sin estrogens have been known to produce tumors, some of them malignant, in five species subprimate animals. 2. Endocrine and possibly liver function tests may be affected by tre ment with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28. Therefore, if such tes are abnormal in a patient taking ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28, is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibrom mata may increase in size. 4. Because these agents may cause some degree of fluid ret tion, conditions which might be influenced by this factor, such as epilepsy, migrain asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough blee ing, and in all cases of irregular bleeding per vaginam, nonfunctional causes should b borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures a indicated. 6. Patients with a history of psychic depression should be carefully observed ar the drug discontinued if the depression recurs to a serious degree. 7. Any possible influenc of prolonged ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy on pituita ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucos tolerance has been observed in a significant percentage of patients on oral contraceptive The mechanism of this decrease is obscure. For this reason, diabetic patients should b carefully observed while receiving ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□2 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatme with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 may mask the onset of th climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/80□21 c ORTHO-NOVUM 1/80□28 therapy when relevant specimens are submitted. 11. Suscep ble women may experience an increase in blood pressure following administration of co traceptive steroids. 12. Cholestatic jaundice has been reported in users of ora contraceptives. If this occurs ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□2 should be discontinued. This condition is more likely to occur in patients who hav experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jau dice of pregnancy should be carefully observed during ORTHO-NOVUM 1/80□21 c ORTHO-NOVUM 1/80□28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and th following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebra thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has bee neither confirmed nor refuted for the following serious adverse reactions: neuro-ocula lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intr abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contrace tives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloa ing), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during an after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundic migraine, rash (allergic), mental depression, change in weight (increase or decrease breast changes (tenderness, enlargement and secretion), changes in cervical erosion an cervical secretions, suppression of lactation when given immediately post-partum, rise i blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contrace tives, an association has been neither confirmed nor refuted: anovulation post-treatmer which tends to occur more frequently in women with a history of menstrual disorder premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrom headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsu ism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepat function—increased sulfobromophthalein retention and other tests; coagulation tests· increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase i platelet aggregability; thyroid function—increase in PBI, and butanol extractable protei bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determin tion.

References: 1. Royal College of General Practitioners: Oral Contraception and Thromb Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolisr in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Do R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembol Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: A Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Co traception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Me *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Wome Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptive and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, an Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, La cet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contrace tives and Health, 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-12 July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients wi Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):68 685, May 1972. **11.** Mann, J.I.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial Infarctic in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:24 245, May 3, 1975. **12.** Mann, J.I.; Inman, W.H.W.: Oral Contraceptives and Death fro Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J. J.; Nora, A. H.: Bir Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Pipe J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl Med *291*(14):697-700, Oct. 3, 1974.

OJ 719-5 R

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Articles to appear in early issues

Incorporation of ^{14}C-l-palmitate into rabbit fetal lipids in vivo
J. J. Biezenski, M.D.
Chicago, Illinois

Cellular hypersensitivity in patients with adenomatous hyperplasia and adenocarcinoma of the endometrium
Sidney Y. Chen, M.D., Carmel J. Cohen, M.D., and David Koffler, M.D.
New York, New York

Immunologic and biological activity of oxytocin in midtrimester pregnancy
Alois Vasicka, M.D., F.A.C.O.G., P. Kumaresan, D.V.M., Ph.D., C. Li, M.D., and J. Scheffs, M.D., F.A.C.O.G.
Brooklyn, New York

Umbilical cord compression associated with amniotomy: Laboratory observations
Steven G. Gabbe, M.D., Bruce B. Ettinger, M.D., Roger K. Freeman, M.D., and Chester B. Martin, M.D.
Los Angeles, California

The effects of dexamethasone on plasma free androgens during the normal menstrual cycle
Moon H. Kim, M.D., Robert L. Rosenfield, M.D., and Caryn Dupon, Ph.D.
Chicago, Illinois

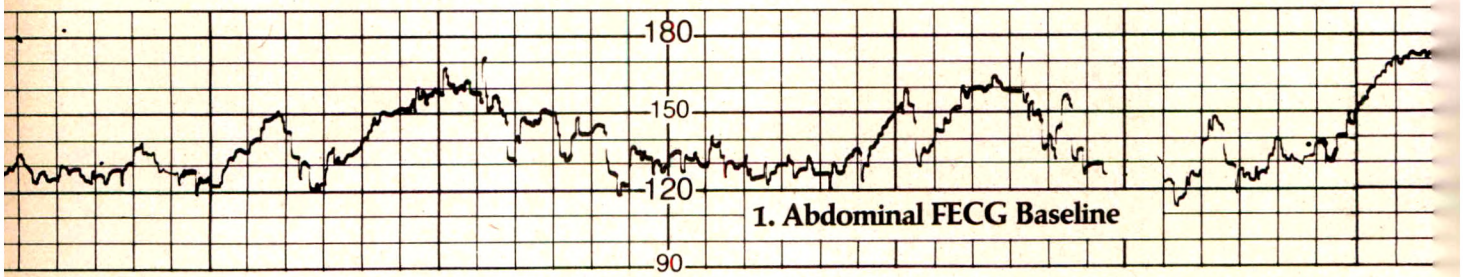
Fetal immune response following prematurely ruptured membranes
Lars L. Cederqvist, Linda C. Francis, Ioannis A. Zervoudakis, Carl G. Becker, and Stephen D. Litwin
New York, New York

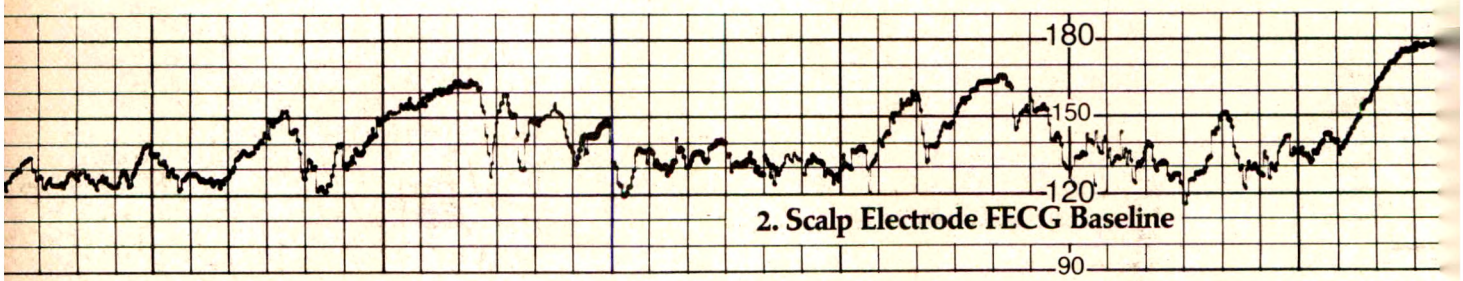
Placental cultures for cytogenetic assessment in saline-aborted fetuses
H. Allen Gardner, M.D., M.Sc., F.R.C.P.(C), E. Martha Wood, B.A., R.T., and Ellyn Stecker, B.A.
Toronto, Ontario, Canada

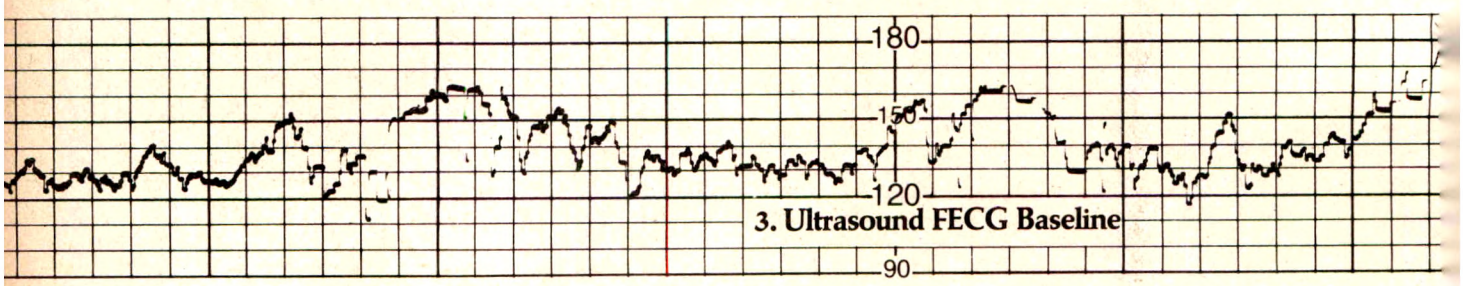
Diagnosis of prolactin-secreting pituitary microadenoma
R. Herbert Wiebe, M.D., Charles B. Hammond, M.D., and Lynn G. Borchert, M.D.
Durham, North Carolina, and Richmond, Virginia

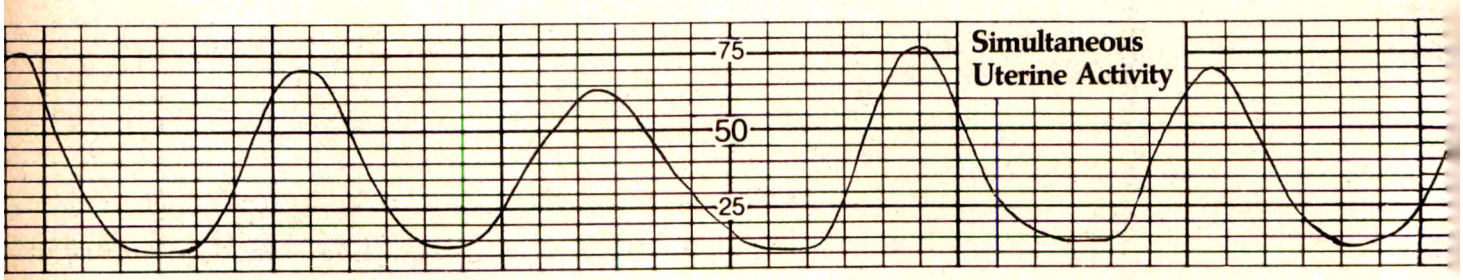
Serum chorionic gonadotropin levels throughout normal pregnancy
Glenn D. Braunstein, M.D., Joan Rasor, M.A., Donald Adler, M.D., Hal Danzer, M.D., and Maclyn E. Wade, M.D.
Los Angeles, California

Happy Birth











Our new Fetal Monitor offers three ways to observe the occasion.

1. Abdominal FECG—Baseline. For years it was only a promising theory. But the B-D Electrodyne Fetal Monitor solves the difficult problem of separating the maternal heart beat from the fetal heart beat—even when the QRS complexes are merged.

Through over 2,500 hours of labor with more than 500 patients, the B-D Electrodyne abdominal ECG method proved itself applicable, on average, for 3 out of 4 fetal monitoring candidates. As you can see in the recordings, accuracy and performance were remarkably close to that of the directly attached scalp electrode.

The B-D Electrodyne Fetal Monitor records contractions simultaneously from a lightweight tocody-

days, America!



nomometer. Trend, digital display of fetal heart rate, and variable speed recorder for FECG and maternal ECG and labor contractions are also included.

2. Scalp Electrode FECG—Baseline. After presentation occurs, and if contraction interference becomes severe, this most reliable of methods may be preferred. The B-D Electrodyne Fetal Monitor switches quickly to this capability.

3. Ultrasonic FECG Baseline. Because the physiology of some patients occasionally prevents the use of abdominal ECG (one out of four cases on average), we offer our Ultrasound Amplifier an an option. Transducer and accessories are included.

Altogether the B-D Electrodyne Fetal Monitor gives you the best of three worlds. And B-D Electrodyne's inservice education and warranty policies are among the best. Let us demonstrate at your place. Please write or call and we'll be glad to make arrangements. B-D Electrodyne, Division of Becton, Dickinson and Company, Route One, Sharon, Massachusetts 02067. (617) 828-9080

B-D ELECTRODYNE
Division of Becton, Dickinson and Company

© Copyright 1976 B-D Electrodyne


Because
you want more
for her
than just
symptomatic
relief...
© OPC 1976

Sultrin
TRADEMARK

Triple Sulfa Cream/Vaginal Tablets

effective against and specific for H. vaginalis

The cause of over 90% of "nonspecific" vaginitis†

effective

based on review by the National Academy of Sciences/National Research Counsel, Sultrin was rated as "effective" against *H. vaginalis*.

prompt symptomatic relief

often within a few days, patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

versatile adjunct in other vaginitides

Sultrin is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

convenient choice of dosage forms

Sultrin comes as a soothing, non-staining and esthetically pleasing cream or convenient vaginal tablets.

Composition: Each SULTRIN Tablet contains sulfathiazole 172.5 mg, sulfacetamide 143.75 mg, and sulfabenzamide 184.0 mg. SULTRIN Triple Sulfa Cream contains sulfathiazole 3.42%, sulfacetamide 2.86%, sulfabenzamide 3.7% and urea 0.64%.
Indications: SULTRIN Tablets and Cream are indicated for treatment of *Haemophilus vaginalis* vaginitis. They may also be used as a deodorant for saprophytic infection following radiation therapy.
Contraindications: Sulfonamide sensitivity and kidney disease.
Dosage: SULTRIN Tablets: One tablet intravaginally before retiring and again in the morning for ten days. This course may be repeated if necessary. SULTRIN Cream: One applicatorful intravaginally twice daily for 4 to 6 days. The dosage may then be reduced one-half to one-quarter.
Supplied: SULTRIN Tablets are available in packages of 20 foil-wrapped tablets with vaginal applicator. SULTRIN Cream is available in 2.75 oz. (78 g) tubes with the ORTHO* Measured-Dose Applicator. OJ 10-6 *TRADEMARK

†Gardner, H.L. and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Ortho



NEW & BETTER

...The all-American Frigi Colposcope

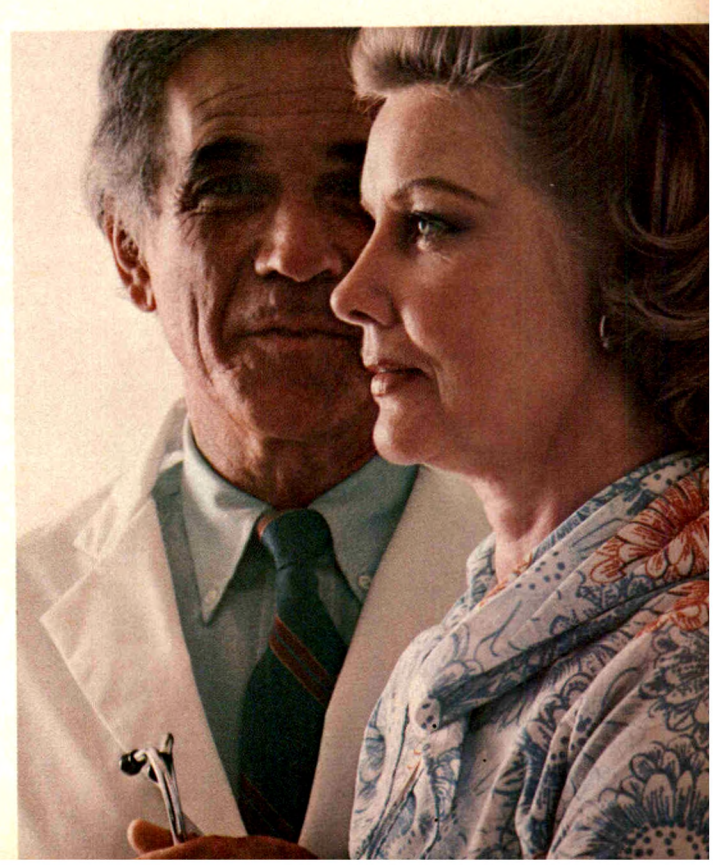
- At half the cost of comparable imports, even including the cost of teaching tube and camera adaptor.
- Superior to the finest German and Japanese models.
- Plus, choices and options to suit your practice.
- Plus sales and service representation in your locale.
- Seeing is believing. See it in your office. Call collect today.

frigitronics®
OF CONNECTICUT INCORPORATED
770 RIVER ROAD, SHELTON, CONNECTICUT 06484
203/929-6321

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
IN THE MENOPAUSE TODAY

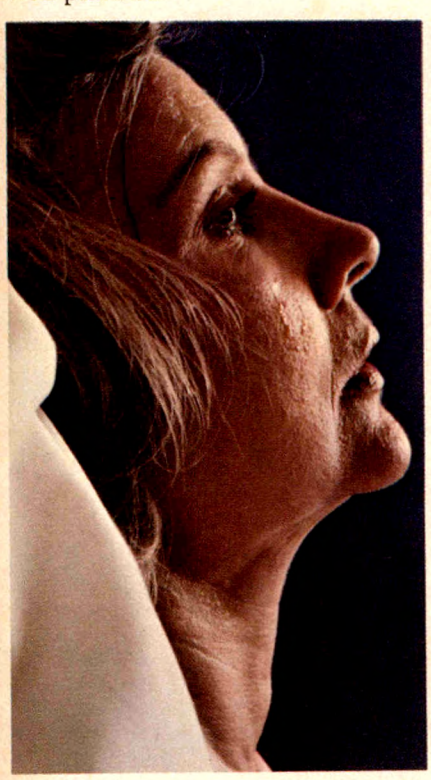
"The height of professional integrity is to prescribe estrogen when needed and indicated, and to withhold it if there is no indication or when a contraindication to its use exists."

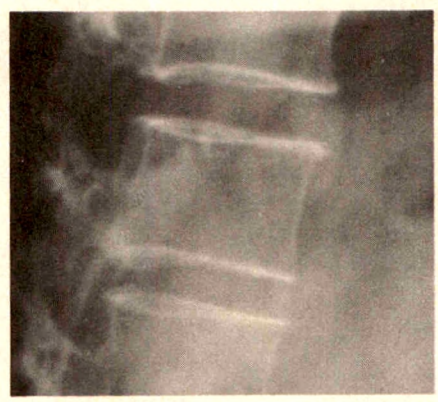
—Barber, H.R.K.:
Editorial, in The Female Patient
1:7 (Mar.) 1976.



Manifestations of estrogen deficiency...

Vasomotor Instability
commonly appearing in the menopause as hot flushes, sweats, palpitations, numbness, and tingling. Hot flushes, a classic symptom of estrogen deficiency, are a clear-cut indication for treatment. The therapeutic goal is well-defined: "...to minimize the intensity of the duration of distressing symptoms as well as to tide the patient over the period of physiologic adjustment. The symptoms vanish in almost all instances if the estrogenic therapy is adequate and well-planned."[1]





Postmenopausal Osteoporosis*
is often related to estrogen deficiency. Effects may not be apparent until a decade or more after the natural menopause, but may be evident in as little as three years after surgical menopause. With the advent of new technics for the accurate measurement of bone density, it has been possible to demonstrate that decrease in mass is related to loss of ovarian function, not age.[2] This has been confirmed by a retrospective study[3] of hysterectomized women with and without oophorectomy.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

Atrophic Vaginitis
often with involvement of related genitourinary structures, is frequently associated with estrogen deficiency. The gradual atrophic changes render vulvovaginal and urethral tissues more susceptible to trauma, inflammation, and secondary infection which may lead to pruritus and pain, dyspareunia, dysuria and incontinence. Replacement therapy helps to restore genitourinary tissue to a healthier, more normal state. The uncomfortable symptoms are often promptly controlled by estrogen therapy.



In addition, surgical menopause presents the signs of abrupt estrogen deficiency in their most acute fashion: not only vasomotor flushes and sweats, but other common symptoms of the menopausal syndrome, as well. These symptoms are usually rapidly relieved by adequate estrogen therapy.

1. Israel, S.L.: Diagnosis and Treatment of Menstrual Disorders and Sterility, ed. 5, New York, Harper & Row, 1967, p. 398.
2. Meema, S., *et al.*: Arch. Intern. Med. *135*:1436 (Nov.) 1975.
3. Aitken, J.M., *et al.*: Br. Med. J. *2*:325 (May 12) 1973.

Management of estrogen deficiency...

Management of estrogen deficiency symptoms includes the appropriate use of estrogen replacement therapy, and requires three basic principles of good medical management: the proper patient...the proper dosage...and the proper precautions.

The Proper Patient...
is, of course, the woman who presents significant symptomatology of estrogen deficiency in the absence of any contraindications. Pretreatment assessment of the patient should include a complete physical examination and careful history-taking to determine personal or familial incidence of carcinoma, hypertension, thromboembolic disorders, or undiagnosed abnormal genital bleeding. Repeatedly, estrogens have been shown to be of benefit in relieving the manifestations of estrogen deficiency. Although the evaluation of estrogen deficiency may be assisted by vaginal cytology, the principal criterion for treatment is still the degree of symptomatology.

The Proper Dosage...
should be the lowest dosage that relieves the patient's symptoms, as determined by empirical trial. With PREMARIN, the usual starting dosage for the common symptoms of the menopause is 1.25 mg per day for three weeks, followed by a one-week rest period. Following an adequate trial period, this dosage may be titrated upward or downward depending upon severity of symptoms and individual patient response. In prophylactic use for the prevention of osteoporosis,* PREMARIN, in conjunction with other recognized measures, may be effective in a dose of 0.625 mg per day, administered cyclically. In advanced osteoporosis, PREMARIN, 1.25 mg per day, is usually the recommended dosage to retard progression and reduce the incidence of further fractures.

The Proper Precautions...
should include cyclic administration—three weeks on, one week off, to avoid prolonged stimulation of the endometrium and breasts; at least annual checkups, including breast and pelvic examinations; and the thorough and prompt investigation of any unexplained vaginal bleeding and/or breast changes. In addition, the need for therapy should be reassessed on an annual basis to determine if estrogen replacement therapy is still required for symptomatic relief.

These precautions are representative of the prudent approach to estrogen replacement therapy.

PREMARIN continues to be highly efficacious in relieving and preventing the physical and physiological consequences of estrogen deficiency. When indicated, and utilizing the appropriate precautions, patients can experience the therapeutic benefits of estrogen replacement therapy today.

Three studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. For further information see "Warnings" in prescribing information.



ESTROGEN REPLACEMENT THERAPY

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

Estrogens obtained exclusively from natural sources

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

See last page of advertisement for revised prescribing information.

Ayerst®

AYERST LABORATORIES
New York, N.Y. 10017

BRIEF SUMMARY

(For full prescribing information, see package circular.)

PREMARIN® Brand of
CONJUGATED ESTROGENS TABLETS, U.S.P.

Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration; however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al.*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:

nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg, in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg, in bottles of 100 and 1,000.

References: 1. Smith, D.C., Prentice, R., Thompson, D.J., and Herrmann, W.L.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. *293*:1164-1167, 1975. 2. Ziel, H.K., and Finkle, W.D.: Increased risk of endometrial carcinoma among users of conjugated estrogens, N. Engl. J. Med. *293*:1167-1170, 1975. 3. Mack, T.M., Pike, M.C., Henderson, B.E., Pfeffer, R.I., Gerkins, V.R., Arthur, M., and Brown, S.: Estrogens and endometrial cancer in a retirement community, submitted for publication.

7642

Ayerst. AYERST LABORATORIES
New York, N.Y. 10017

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
contains natural estrogens exclusively

Needle puncture of fetus: A complication of second-trimester amniocentesis

DIANE L. BROOME, M.D.
MIRIAM G. WILSON, M.D.
BENNETT WEISS, M.D.
BONNIE KELLOGG, P.H.N.
Los Angeles, California

Needle puncture of the fetus has rarely been reported with midtrimester amniocentesis. This paper contains the report of five cases of needle scars in infants born after second-trimester amniocentesis for prenatal diagnosis of fetal genetic disorders. Since this complication may be more frequent than has been previously believed, there is the possibility that damage to the fetus may occur. It is suggested that the products of all abortions and all live-born and stillborn infants delivered following amniocentesis should be examined for evidence of injury.

ALTHOUGH SOMETIMES occurring in third-trimester amniocentesis, needle puncture of the fetus has rarely been reported with midtrimester amniocenteses. We are reporting needle scars in five infants born after second-trimester amniocentesis for prenatal diagnosis of fetal genetic disorders. Since this complication is apparently not rare, there is the possibility that damage to the fetus may occur, depending on which part of the body is penetrated.

Four of these children (Case 5 was contributed by a neighboring institution) were seen at our medical center from 1972 to 1976 in a routine amniocentesis follow-up program. The indication for amniocentesis in these cases was an increased risk for fetal chromosomal abnormality. All the amniocenteses were done by the same faculty obstetrician who had done these procedures since 1969 and who had extensive prior experience in third-trimester amniocentesis for management of erythroblastosis.

Amniocentesis was done between the sixteenth and seventeenth postmenstrual weeks of pregnancy. A disposable 20 gauge, 3½ inch, styleted spinal needle was used for all of these procedures. In all instances, analysis of the cultured amniotic fluid cells showed a normal karyotype concordant with the sex of the child. All children have grown and developed normally.

From the Department of Pediatrics, Genetics Division, and the Department of Obstetrics-Gynecology, Los Angeles County–University of Southern California Medical Center.

Received for publication June 9, 1976.

Accepted June 23, 1976.

Reprint requests: Dr. Diane L. Broome, 1G-30 General Laboratory Bldg. for Basic and Clinical Research, Los Angeles County–University of Southern California Medical Center, 1129 N. State St., Los Angeles, California 90033.

Case reports

Patient M. D. (Case 1). A diagnostic amniocentesis was performed at 17½ weeks of pregnancy on this 35-year-old Caucasian woman who was gravida 8 and para 5 and had 2 abortions. The amniocentesis was performed easily, and a single insertion yielded at first

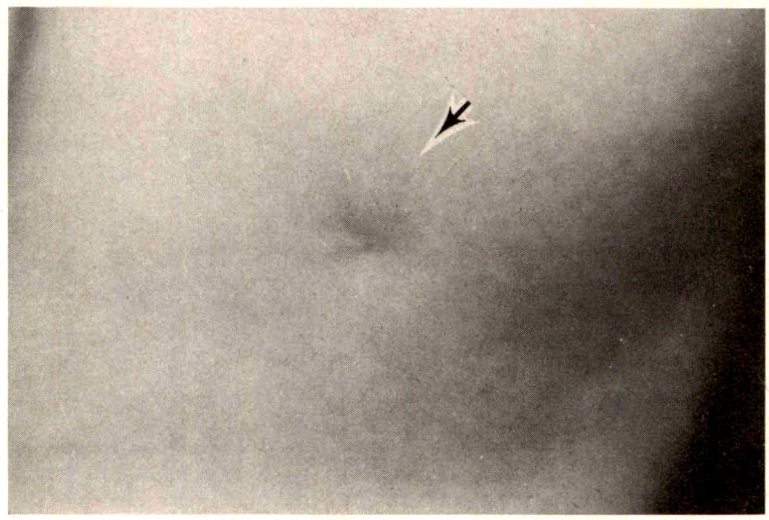


Fig. 1. Case 1. Depressed scar on arm.

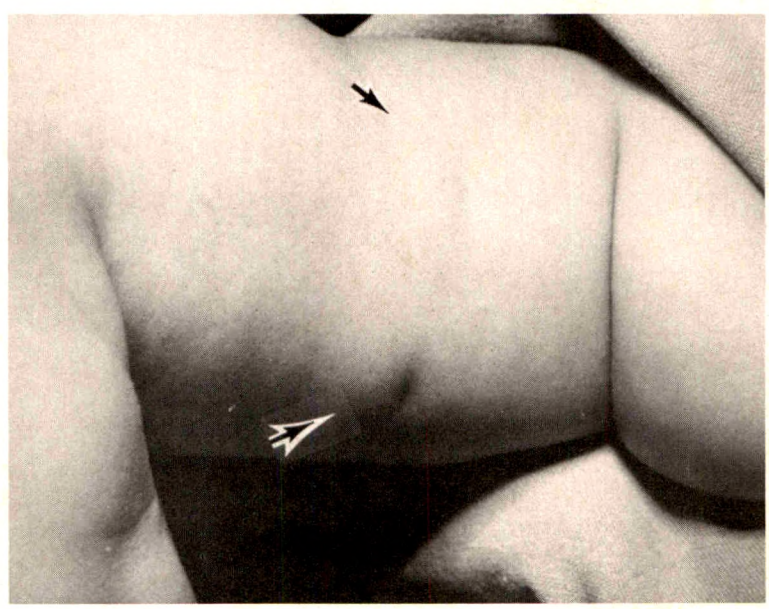


Fig. 2. Case 2. Scars on arm.

15 c.c. of clear yellow fluid followed by 25 c.c. of blood-tinged fluid. The pregnancy progressed to a normal term vaginal delivery of a healthy female infant, weighing 4,876 grams.

At birth, the mother asked about the scar on the infant's arm and was told by the physicians that the infant had received no injections and there was no apparent reason for the skin lesion. The child had no limitation of arm movement, and the skin mark became less noticeable with age.

A physical examination at nine months showed normal findings except for scars on the infant's right upper arm (Fig. 1). A small depressed scar was found on the anterior aspect of the proximal upper arm and a small linear scar extended 1.5 cm. posteriorly from the depression. The circumferences of the arms were equal. A radiograph of the right upper arm revealed increased soft-tissue density consistent with subcutaneous scar formation.

Patient V. D. (Case 2). A diagnostic amniocentesis was performed at the sixteenth week of pregnancy on a 23-year-old Mexican-American woman who was gravida 5 and para 3 with one abortion. The second child had Down's syndrome. Amniocentesis in the fourth pregnancy had yielded a normal chromosome analysis.

In the fifth pregnancy, amniocentesis was performed without difficulty, and 40 c.c. of clear, straw-colored

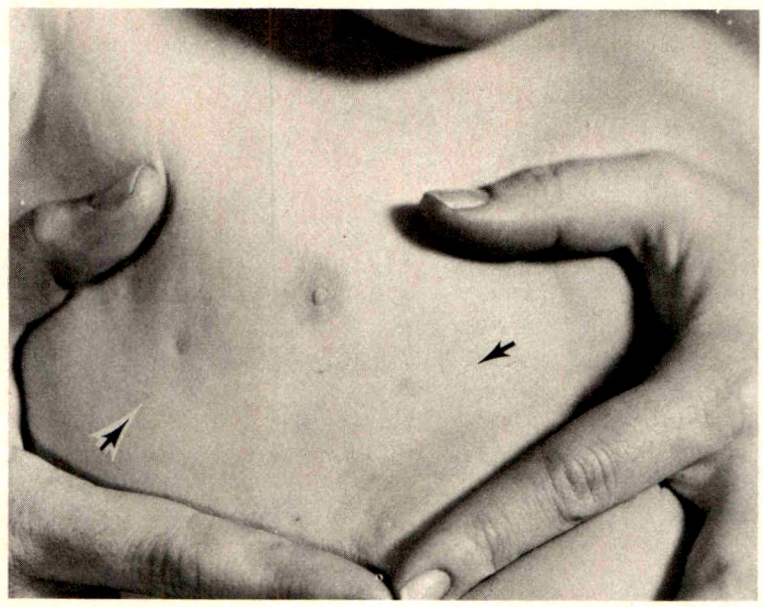


Fig. 3. Case 3. Scars on right anterior chest wall.

fluid was withdrawn. Immediately afterward, the patient complained of severe cramping which soon subsided.

A female infant weighing 3,284 grams was born at term by a normal vaginal delivery. The mother noted scars on the arm and chest at birth but did not bring them to the attention of a physician. The child used both arms equally.

Physical examination of the infant at nine months of age showed scars on the arm and chest. The left arm had two indentations 1.5 cm. apart (Fig. 2) and two smaller indentations on the anterior chest wall 1 cm. apart. When the left arm was brought next to the chest in a simulated fetal position, the four scars were in a straight line. Radiographs revealed soft-tissue density underlying the scars on the arm.

Patient J. B. (Case 3). Amniocentesis was performed on a 24-year-old Caucasian woman whose first child had a structural chromosome anomaly (46,XX,18q−). The karyotypes of the parents were normal. The woman had had no other pregnancies.

Amniocentesis at 16 weeks of pregnancy required three insertions before 40 c.c. of grossly bloody fluid was obtained. Since cell growth was inadequate in the first culture, the amniocentesis was repeated two weeks later, at which time 40 c.c. of amniotic fluid tinged with blood was obtained without difficulty. The pregnancy progressed to term, at which time a female infant weighing 3,190 grams was born by normal vaginal delivery.

On physical examination at eight and a half months the infant appeared normal. When she was seen again at three years, scars were noted on the chest and thigh. The mother said that these marks had been present since birth. There were two depressions on the right anterior chest wall. One scar was lateral and the other was medial to the nipple (Fig. 3). There was another indentation on the left posterior thigh (Fig. 4). When the child was placed in a fetal position, all three indentations were in a straight line.

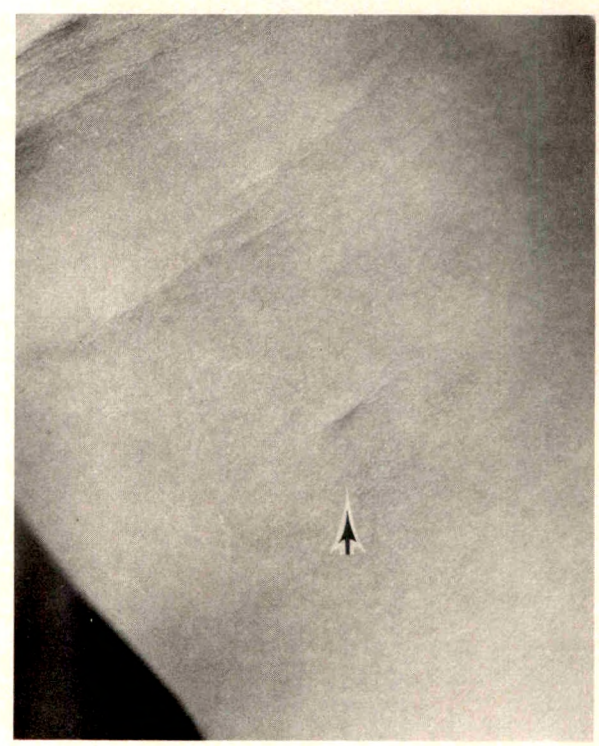


Fig. 4. Case 3. Scar on left posterior thigh.

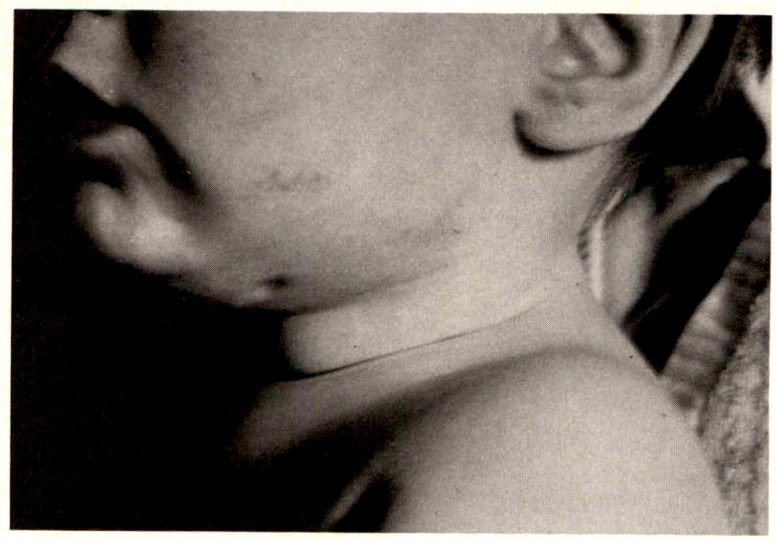


Fig. 5. Case 4. Scar under chin.

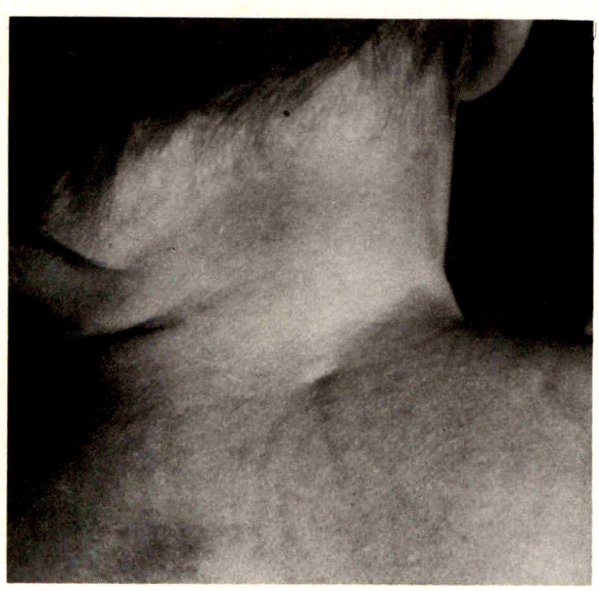


Fig. 6. Case 4. Scar on neck.

Patient M. B. (Case 4). Amniocentesis was performed in the seventeenth week of pregnancy on a 28-year-old Caucasian woman who was gravida 5 and para 3. She had had one abortion and one neonatal death. Amniocentesis was done because of a family history of Down's syndrome. The mother's sister had Down's syndrome with a karyotype of 46,XX/47,XX,+21 and the mother's maternal aunt had Down's syndrome (no chromosome analysis). Karyotypes of both parents were normal.

Ultrasonography was performed prior to amniocentesis. Clear yellow fluid (40 c.c.) was slowly withdrawn. Pregnancy progressed to a normal delivery of a 3,374 gram term female infant.

When the infant was seen at nine months, scars under the left jaw (Fig. 5) and a depressed scar just right of the midline on the posterior neck were noted (Fig. 6). These scars had been seen by the mother at birth.

Case 5. Another infant with needle marks has been reported to us.* In this instance, amniocentesis was performed on a 26-year-old Caucasian woman in the sixteenth week of pregnancy. The mother had been delivered of a child with Down's syndrome two years previously.

The first amniocentesis was done without difficulty, and 39 c.c. of clear yellow fluid was obtained. Because of slow cell growth, the procedure was repeated two weeks later, at which time 40 c.c. of clear yellow fluid was obtained without difficulty. Ultrasonography was done prior to amniocentesis in both procedures.

Pregnancy proceeded to delivery of a 2,964 gram female infant. The mother brought the child at two months of age for investigation of several scars on the buttocks and legs.

Physical examination was normal except for three scars. One on the lateral right buttock was 1 mm. in depth and 2 mm. in diameter (Fig. 7). Another scar was found on the left labium majora, and a third was close by on the medial aspect of the left thigh.

Comment

Fetal injury due to midpregnancy amniocentesis has not been reported as a significant hazard,[1-8] although injury to the fetus during third-trimester amniocentesis has included pneumothorax,[9] pneumopericardium, splenic rupture, skin scars, eye trauma,[10] and

*Dr. Kenneth Dumars provided us with details and photographs of this case.

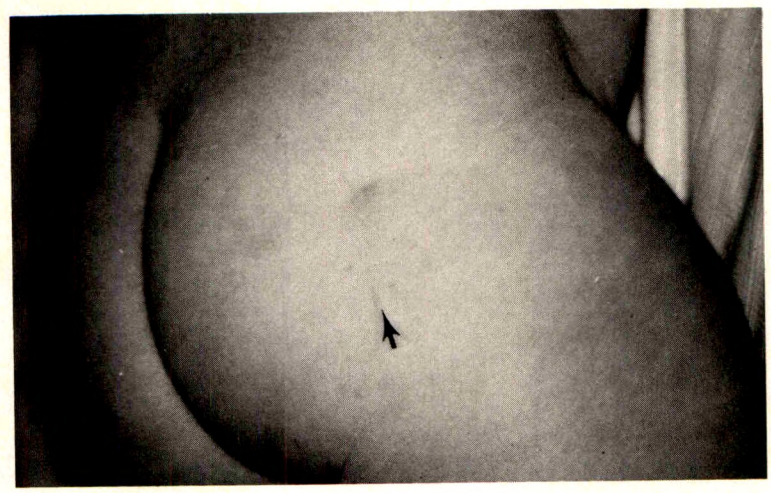


Fig. 7. Case 5. Scar on buttock.

recently an arteriovenous fistula.[11] According to preliminary reports of a prospective study by the National Institute of Child Health and Human Development,[2, 3] amniocentesis in the second trimester of pregnancy appears to be safe for mother and child. The outcome of pregnancy in 1,040 women with midpregnancy amniocentesis for prenatal diagnosis was compared to that of 992 matched control pregnancies. There were no significant differences in maternal morbidity, fetal death or abortion, prematurity, neonatal complications, or congenital defects in the infants. Specifically, there was no mention of any scars in the infants possibly resulting from needle penetrations in utero.[3]

We have now been able to examine about 100 infants born after amniocentesis for prenatal diagnosis. Four of these infants showed scars interpreted to represent residual scarring after needle puncture in utero.[12] The interpretation was based on the observation that the scars were not in the usual position of congenital sinus tracts, and in two instances multiple scars fell in a straight line when the infant was placed into a simulated fetal position. The case reported to us from a neighboring medical school further substantiated that needle puncture of the fetus may occur during a midpregnancy amniocentesis. There are previous reports of a scar on the buttocks in a child born after midpregnancy amniocentesis[1] and gangrene of a fetal limb seen in a therapeutically aborted fetus following another midpregnancy amniocentesis.[8]

The use of ultrasonography, which is now routinely done prior to amniocentesis in our institution, may reduce the likelihood of needle puncture of the fetal head, particularly if performed just before the amniocentesis and before the mother changes posture.

We now include disclosure of this hazard while obtaining informed consent from the parents prior to amniocentesis. In this regard, it is noteworthy that one set of parents (Case 2) elected amniocentesis for the next pregnancy following the birth of one of the children reported here.

Needle puncture of the fetus during second-trimester amniocentesis is a hazard of unknown magnitude. The scars in the children described here were minor and, indeed, were overlooked in the first examination of one of the children. However, the possibility exists that a vital fetal part, such as the eye or a major blood vessel, might be punctured with interference of full development of a part of the body. It is of the utmost importance that all abortions and stilllbirths occurring after amniocentesis, as well as infants born after the procedure, be carefully examined for evidence of fetal injury.

We wish to acknowledge the contributions of Drs. Kenneth Dumars, Allen Iseri, and Nancy Shinno.

REFERENCES

1. Allen, H. H., Sergovich, F., Stuart, E. M., et al.: Infants undergoing antenatal genetic diagnosis: A preliminary report, Am. J. Obstet. Gynecol. **118:** 310, 1974.
2. Culliton, B. J.: Amniocentesis: HEW backs test for prenatal diagnosis of diseases, Science **190:** 537, 1975.
3. Milunsky, A.: Risk of amniocentesis for prenatal diagnosis, N. Engl. J. Med. **293:** 932, 1975.
4. Nadler, H. L., and Gerbie, A. B.: Role of amniocentesis in the intrauterine detection of genetic disorders, N. Engl. J. Med. **282:** 596, 1970.
5. Creasman, W. T., Lawrence, R. A., and Thiede, H. A.: Fetal complications of amniocentesis, J. A. M. A. **204:** 91, 1968.
6. Hirschhorn, K.: The role and the hazards of amniocentesis, Ann. N. Y. Acad. Sci. **240:** 117, 1975.

7. Robinson, A., Bowes, W., Droegemueller, W., et al.: Intrauterine diagnosis: Potential complications, AM. J. OBSTET. GYNECOL. **116:** 937, 1973.
8. Lamb, M. P.: Gangrene of a fetal limb due to amniocentesis, J. Obstet. Gynaecol. Br. Commonw. **82:** 829, 1975.
9. Cook, L. N., Shott, R. J., and Andrews, B. F.: Fetal complications of diagnostic amniocentesis: A review and report of a case with pneumothorax, Pediatrics **53:** 421, 1974.
10. Cross, H. E., and Maumenee, A. E.: Ocular trauma during amniocentesis, Ophthalmologica **90:** 303, 1973.
11. Gottdiener, J. S., Ellison, R. C., and Lorenzo, R. L.: Arteriovenous fistula after fetal penetration at amniocentesis. N. Engl. J. Med. **293:** 1302, 1975.
12. Broome, D. L., Kellogg, B., Weiss, B. A., and Wilson, M. G.: Needle puncture of the fetus during amniocentesis, Lancet **2:** 604, 1975.

Circulatory response to atropine in sheep fetus

TSUYOMU IKENOUE, M.D.*
EDWARD J. QUILLIGAN, M.D.
YUJI MURATA, M.D.
Los Angeles, California

Atropine was given to the semichronic sheep fetus intravenously. Fetal heart rate, fetal perfusion pressure, and carotid blood flow increased. Cerebral blood flow was measured with the radioactive microsphere technique. Atropine was capable of increasing the cerebral blood flow. Elevation of carbon dioxide also caused an increase in cerebral blood flow, adding to the effect of atropine.

WHEN ATROPINE is given to fetuses of different gestational ages, the fetal circulatory system responds to this cholinergic blockade in various fashions according to the stage of vagal maturation.[1-3] Atropine distribution to the fetal central nervous system is small in comparison with the heart.[4] It has been suggested that the fetal cardiac response in rats to maternal administration of atropine is a peripheral response rather than a central one based on the assumption that the fetal central nervous system and heart possess similar thresholds to the anticholinergic actions of atropine.[4] As a matter of fact, Vapaavouri and associates[2] have shown in sheep that there is no end-organ sensitivity change as gestation progresses. Nuwayhid and associates[3] stimulated the afferent vagal reflex and noted the presence of a circulatory response even in immature sheep fetuses as early as 65 days of gestation, although there is little parasympathetic tone on resting fetal heart rate (FHR) and other circulatory functions at this age. It is possible that a vagally stimulated circulatory response may play an important role in fetal adjustment, particularly when the fetus is under stress, not unlike the diving reflex of the seal,[5] and these reflexes having been abolished by atropine would not enhance fetal homeostasis.

Dunnihoo and Quilligan,[6] using a radioactive microsphere technique, noted a reciprocal distribution between the cerebral and extracerebral circuits with increasing carbon dioxide tensions, whereas there were no appreciable changes in the estimated bilateral carotid flow over a broad range of carbon dioxide tensions[6, 7] in semichronic fetal lamb preparations. In sheep, not in man, there is an anatomic interconnection between the cerebral and extracerebral vascular circuit (rete mirabile) and mainly through this interconnection, the fetal cephalic blood flow distribution appears to be modified in some situations. In the present study we looked at the effect of atropine sulfate on a portion of the circulatory system in the sheep fetus in utero. This was also extended to observe the response of the cephalic circulatory circuits to the elevation of the carbon dioxide tensions under the influence of atropine sulfate.

Materials and methods

Eight Dorset and Rambouillet sheep of about 112 to 144 days' gestation (estimated from Barcroft measurements) were kept in an air-conditioned stall for several days, starved for 48 to 72 hours, and given water ad libitum. About 30 minutes prior to surgery, 5 mg. of chlorpromazine* was given to the ewe intravenously. The surgery was performed under local 1 per cent lidocaine† anesthesia. Through a small

From the Department of Obstetrics and Gynecology, Los Angeles County–University of Southern California Medical Center.

Supported in part by Grant R01HD07377.

Received for publication October 3, 1975.

Revised March 22, 1975.

Accepted April 9, 1976.

Reprint requests: E. J. Quilligan, M.D., 1240 N. Mission Rd., Los Angeles, California 90033.

**Fellow, Perinatal Biology Section, supported in part by Rotary Foundation, 1600 Ridge Ave., Evanston, Illinois 60201. Present address, Kagoshima Municipal Hospital, Department of Obstetrics and Gynecology, Kagoshima, Japan.*

*Thorazine, brand of chlorpromazine hydrochloride, Smith Kline & French Laboratories, Philadelphia, Pennsylvania.

†Lidocaine hydrochloride injection, U.S.P. 1 per cent, Invenex Division of the Mongul Corporation, Chagrin Falls, Ohio.

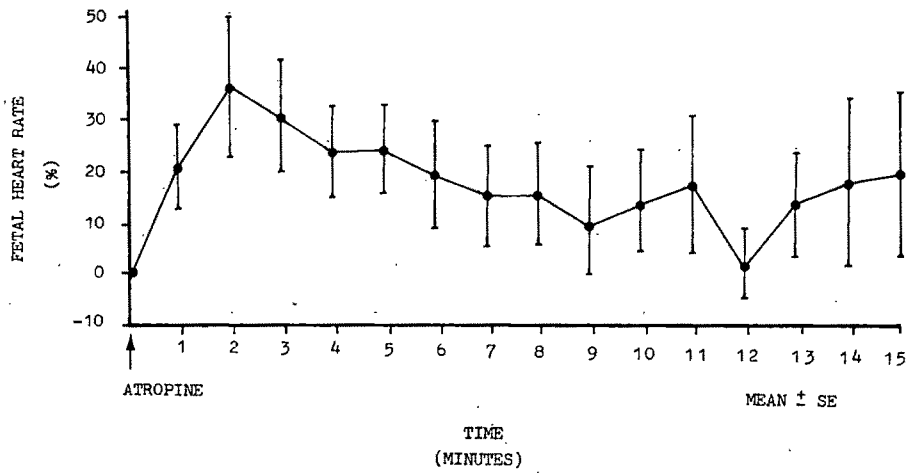


Fig. 1. Per cent changes from control values in fetal heart rate (mean ± S.E.).

uterine incision, one of the hindlimbs was pulled out and the fetal femoral artery and vein were catheterized with siliconized polyethylene plastic catheters (P.E. 50, inside diameter 0.023 inch, outside diameter 0.038 inch.)

After returning the leg with the two catheters in place, the uterine incision was closed. Another hysterotomy was made and the fetal head delivered into a warm, saline-filled rubber glove. Silver–silver chloride fetal electrocardiogram electrodes were implanted and a Micron flow probe* was placed around one carotid artery. A P.E. 50 polyethylene catheter was inserted into an external maxillary branch of the jugular vein for the venous pressure determination. A siliconized P.E. 190 polyethylene catheter (inside diameter 0.047 inch, outside diameter 0.067 inch) was placed in the amniotic cavity. The fetus was returned to the intrauterine cavity and the uterus and abdominal wall were closed. The lost amniotic fluid was replaced with warm saline containing 1.0 million units of penicillin via the amniotic catheter. The maternal femoral artery was cannulated with siliconized P.E. 190 polyethylene catheter. All the catheters and cables were tunneled to the left flank of the ewe, where they emerged through a stab wound. All the catheters except the amniotic catheter were flushed continuously with heparinized saline at the rate of 2 drops per minute. Both the mother and fetus were allowed to recover for at least 24 hours after the surgery in the cage. Alfalfa and water were given ad libitum.

The experiment was performed 24 hours after the surgery (one experiment, 105S, was done 7 days after the surgery) while the ewe was resting quietly in the cage. The fetal silver–silver chloride electrodes were connected to a cardiotachometer to obtain the fetal heart rate and the flow probe was connected to a Medcon flowmeter* to record carotid blood flow. Fetal arterial blood pressure, fetal venous pressure, and maternal arterial blood pressure were continuously measured via catheters attached to appropriate transducers. All the above information was recorded on a seven-channel recorder.† Periodic blood-gas samples were obtained in siliconized heparinized glass syringes via both fetal and maternal catheters for determination of P_{O_2} and P_{CO_2} on IL blood gas meter, pH and base excess (BE) on an Astrup pH meter. All values were corrected to 39° C., approximating the intrauterine temperature.

Six animals were given the first radioactive microsphere (chromium-51)‡ before the administration of 0.15 mg. of atropine sulfate via the fetal femoral vein catheter and the second radioactive microsphere (cerium-141) was given after the atropine injection. The fetal heart rate, fetal arterial blood pressure, fetal venous pressure, and fetal carotid blood flow were measured continuously throughout the whole experiment. A 15 minute period before atropine, during which ^{51}Cr was given, was taken as a control period. For the succeeding 10 to 15 minutes after the atropine injection, each parameter was determined to compare it with that of the previous control period. The determinations were made at 1 minute intervals and then averaged over the observed period in each experiment.

Two animals were atropinized with 0.15 mg. of

*Micron Instruments, Inc., Los Angeles, California.

*Micron R C 1000 Electromagnetic Blood Flow Meter, Los Angeles, California.

†Brush Mark 200 Recorder, Brush Instruments Division, Clevite, Cleveland, Ohio.

‡Minnesota Mining and Manufacturing, St. Paul, Minnesota.

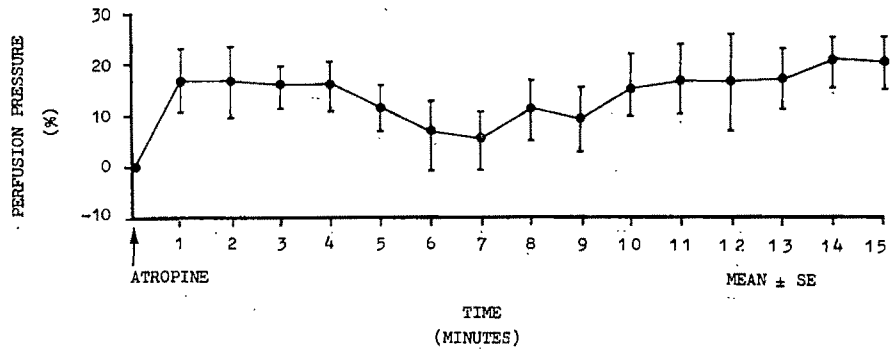


Fig. 2. Per cent changes from control values in perfusion pressure (mean ± S.E.).

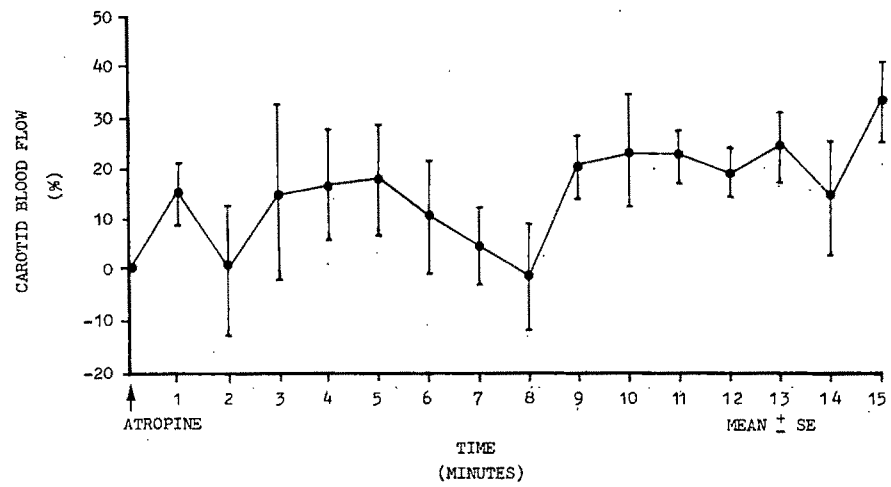


Fig. 3. Per cent changes from control values in carotid blood flow (mean ± S.E.).

atropine sulfate and then the first radioactive microsphere, ^{51}Cr, was given, After a stabilizing period, a gas mixture of 20 per cent CO_2–20 per cent O_2 balanced with N_2 was given via a maternal endotracheal tube placed through a tracheotomy wound which had been made before the experiment started. This gas mixture was given for at least 5 minutes to obtain a high maternal and fetal carbon dioxide elevation. At the end of the CO_2 administration, the second microsphere, ^{141}Ce, was injected and blood-gas samples were obtained. The period between the atropine injection and the start of administration of the CO_2-gas mixture was taken as the baseline control period. The period when the CO_2-gas mixture was given was compared with the baseline control period.

The distribution of the radioactive microspheres in the intra- or extracerebral structures was calculated by the same procedure mentioned by Dunnihoo and Quilligan[6] and Dunnihoo[8] previously. The estimated blood flow and resistance were also calculated on cerebral or extracerebral structures as mentioned in the earlier publications from our laboratory.[6, 8]

Results

The physiologic data from the atropine study are listed in Table I. The baseline fetal heart rate after 0.15 mg. of atropine sulfate rose from a mean of 148.1 b.p.m. (range, 107 to 194 b.p.m.) to 173.2 b.p.m. (range, 128.6 to 201.5 b.p.m.) ($P < 0.05$, paired t test). Two out of eight animals showed a small decrease of the baseline heart rate after the atropine injection (105S and 106S) but the changes of fetal heart rate were minimal, from 194.4 to 186.9 and from 140.9 to 128.6 b.p.m., respectively. The maximum elevation of the fetal heart rate in these two cases after atropine injection was higher than the control values although the duration of this higher baseline was short. The stabilized elevated baseline heart rates were achieved within a minute after atropine injection in all cases (Fig. 1).

The perfusion pressure was approximated by subtracting the jugular vein pressure from the mean arterial pressure. All eight fetuses showed a small but constant increase of perfusion pressure ($P < 0.01$, paired t test). The increase of the mean of the eight

Table I. Physiologic data before and after atropine (S.E. of the mean)

	103S	*104S*	*105S*	*106S*	*107S*
Gest. age (days)	142	144	122	144	140
pH	7.33 7.30	7.37 7.38	7.28 7.30	7.38 7.39	7.38 7.39
Po_2	21.5 17.3	22.8 19.0	11.5 12.0	18.0 17.0	21.0 21.0
Pco_2	39.3 44.5	47.5 45.0	53.3 50.5	51.3 66.5	53.5 55.5
BE	−0.8 −1.4	+3.7 +3.8	−0.7 −1.3	+3.5 +1.9	+3.3 +2.5
FHR (b.p.m.)	107.0 (8.0) 152.0 (16.9)	131.1 (2.4) 152.0 (0.9)	194.4 (2.6) 186.9 (0.7)	140.9 (1.2) 128.6 (4.8)	161.1 (1.7) 199.0 (1.4)
Perf. Pr. (mm. Hg)	39.9 (1.4) 51.7 (1.0)	40.1 (1.2) 49.6 (1.0)	36.8 (1.4) 38.8 (1.2)	43.2 (0.6) 50.7 (0.7)	31.5 (0.6) 32.4 (0.6)
Unilat. carotid flow (ml./min.)	46.6 (3.5) 48.0 (4.5)	39.0 (3.2) 42.3 (2.6)	22.6 (0.7) 29.9 (0.6)	No Data	No Data
Cerebral dist. (%)	75.0 85.0	85.2 87.5	72.9 71.4	75.5 73.6	81.6 83.8
Extracereb. dist. (%)	25.0 15.0	14.8 12.5	27.1 28.6	24.5 26.4	18.4 16.2
Cerebral flow (ml./min./100 Gm.)	128.7 150.2	125.6 139.9	76.2 98.8	No Data	No Data
Extracereb. flow (ml./min./100 Gm.)	7.9 4.9	3.8 3.5	5.7 8.0	No Data	No Data
Cereb. resist (mm. Hg/ml./min./100 Gm.)	0.31 0.34	0.32 0.35	0.48 0.39	No Data	No Data
Extracereb. res. (mm. Hg/ml./min./100 Gm.)	5.05 10.55	10.55 14.17	6.46 4.85	No Data	No Data

fetuses was from 41.8 mm. Hg (range, 31.5 to 52.2 mm. Hg) to 47.6 mm. Hg (range, 32.4 to 54.9 mm. Hg) (Fig. 2).

Six animals were available for determination of the carotid blood flow before and after atropine injection. Although there was an unexpectedly high carotid blood flow in one fetus (110S), all of the fetuses showed a trend of increasing the carotid blood flow, from a mean of 47.8 ml. per minute, unilateral (range, 22.6 to 108.1 ml. per minute) to 52.7 ml. per minute (range, 29.9 to 116.8 ml. per minute) ($P < 0.05$, paired t test) (Fig. 3).

With the use of two different kinds of radioactive microspheres (^{51}Cr and ^{141}Ce), six paired observations were made on cephalic blood flow distribution. The distribution between the cerebral and extracerebral structures remained in almost the same proportion as that of the control period, even under the influence of atropine. The cerebral blood flow distribution of the control period was 79.1 per cent (range, 72.9 to 85.2 per cent) and that under the atropine effect was 81.3 per cent (range, 71.4 to 87.5 per cent) and the extracerebral blood flow distribution was 20.9 per cent (range, 14.8 to 27.1 per cent) before atropine and 18.8 per cent (range, 12.5 to 28.6 per cent) after atropine. Neither structure showed any statistically significant changes.

Only four paired observations of the effect of atropine on cerebral and extracerebral blood flow were made. The individual increase of cerebral blood flow after atropine injection varied from 14.3 to 34.8 ml. per minute per 100 Gm. and all four animals showed this increase of the cerebral blood flow. There were, however, no consistent directions of the change of extracerebral blood flow in these four animals, thus the extracerebral blood flow appears to be unchanged (Fig. 4).

Vascular resistance of the cephalic region was calculated by dividing the perfusion pressure by cerebral or extracerebral blood flow, respectively. On four fetuses, the cephalic vascular resistances were calculated. Atropine injection produced little change in the cerebral vascular resistance. The behavior of the extracerebral vascular resistance varied. In two relatively mature fetuses, an appreciable increase was noted; in the other two relatively younger fetuses, the values remained almost the same.

108S	*110S*	*111S*	*Mean (S.E.)*
112	128	135	
7.27 / 7.25	7.44 / 7.43	7.41 / 7.42	7.35 / 7.35
15.0 / 15.5	16.0 / 15.0	18.0 / 21.0	18.0 (1.3) / 17.2 (1.1)
47.3 / 48.3	45.0 / 52.0	46.5 / 47.0	48.0 (1.7) / 51.2 (2.5)
−6.7 / −9.4	+2.9 / +3.5	+3.8 / +2.6	+1.2 (1.3) / +0.3 (1.6)
108.5 (2.3) / 185.1 (2.2)	165.7 (3.1) / 181.1 (5.5)	175.9 (4.7) / 201.5 (3.5)	148.1 (11.2) / 173.2 (9.2)
40.4 (2.9) / 47.9 (1.5)	52.2 (0.9) / 54.9 (1.3)	50.1 (1.0) / 54.5 (0.6)	41.8 (2.4) / 47.6 (2.8)
25.2 (0.9) / 32.3 (1.1)	108.1 (1.7) / 116.8 (2.4)	45.3 (3.7) / 47.0 (1.1)	47.8 (12.7) / 52.7 (13.2)
84.2 / 86.2			79.1 (2.1) / 81.3 (2.8)
15.8 / 13.8			20.9 (2.1) / 18.8 (2.8)
102.1 / 136.9			108.2 (12.2) / 131.5 (11.3)
5.9 / 6.8			5.8 (0.8) / 5.8 (1.0)
0.40 / 0.35			0.38 (0.04) / 0.36 (0.01)
6.85 / 7.10			7.23 (1.2) / 9.17 (2.0)

Fetal arterial pH, P_{O_2} and P_{CO_2} values did not change significantly throughout the experiment. The base excess decreased significantly but this change occurred within normal limits (1.2 to 0.3 mEq. per liter). Two animals were studied to determine the effect of elevation of carbon dioxide tension on fetal cerebral circulation under the influence of atropine. The physiologic data are listed in Table II. In these two animals, we were able to increase the fetal arterial P_{CO_2} from 52 to 84 mm. Hg and from 46 to 75 mm. Hg, respectively, with a 20 per cent CO_2 and 20 per cent O_2 gas mixture.

There was an obvious increase of cerebral blood flow distribution accompanied by a reciprocal decrease in extracerebral blood flow distribution as the carbon dioxide tensions were elevated. The cerebral blood flow during carbon dioxide administration also showed a significant increase. The increases were 1.66 and 1.80 ml. per minute per 100 Gm. of brain for each millimeter of mercury increase in carbon dioxide tensions. Concomitantly, the extracerebral blood flow decreased as the cerebral blood flow increased. A remarkable increase in the vascular resistance occurred in the extracerebral circulation, not in the cerebral circulation. There was no appreciable change in carotid blood flow as the arterial blood carbon dioxide increased.

Comment

The present data obtained from the unanesthetized semichronic fetal lamb preparations showed an effect of atropine sulfate on the fetal circulation and also showed the alteration of the cephalic blood flow distribution caused by the elevation of carbon dioxide tensions under the influence of atropine.

The effect of atropine on the fetal heart rate has been studied by some investigators. Schifferli and Caldeyro-Barcia[1] gave 2 mg. of atropine sulfate to pregnant women ranging from 14 to 41 weeks of gestation and observed a good correlation between the gestational age and the postatropine fetal heart rate increase. They also observed that there is no influence of gestational age on the postatropine fetal heart rate. In nonmedicated fetuses they showed a decrease in the fetal heart rate throughout pregnancy. From these findings, they suggested that there is an increase in vagal tone with fetal maturation and also documented a detectable cardiomoderator vagal tone even at 15 weeks of pregnancy. Boddy and others[9] noted in their chronic fetal lamb preparation that the fetal arterial pressure rises and fetal heart rate falls with increasing age. They related this increased arterial pressure to the decreasing fetal heart rate near term.

Nuwayhid and others,[3] using fetal lamb preparations (five chronic and nine acute, gestational ages range 60 to 160 days) tried to block the cholinergic stimuli by giving 0.2 to 0.3 mg. per kilogram of atropine intravenously. They showed no appreciable change in the resting heart rate in the fetuses weighing between 300 and 1,500 grams and a slight increase (4 per cent increase) in the fetuses weighing between 1,600 and 2,500 grams. The mature fetuses had an average of a 10 per cent increase. They tried to stimulate the afferent vagal pathways by applying the Bezold-Jarish reflex (veratridine, 3 to 40 μg per kilogram) and atrial stretch recorder stimulation was tried by using 4 to 5 ml. rapid bolus injections of maternal blood or saline. The fetal circulatory responses varied according to the gestational age and maturity, but they were blocked by the atropine injection regardless of the gestational age. They suggested that when the fetal heart rate is vagally depressed, atropine injection restores the fetal heart rate to control levels irrespective of the fetal age, whereas little parasympathetic tone on the resting heart rate was demonstrated.

According to Vapaavouri and others[2] (using the chronic fetal lamb preparation), atropine produces a maximum response by 120 days' gestation with little

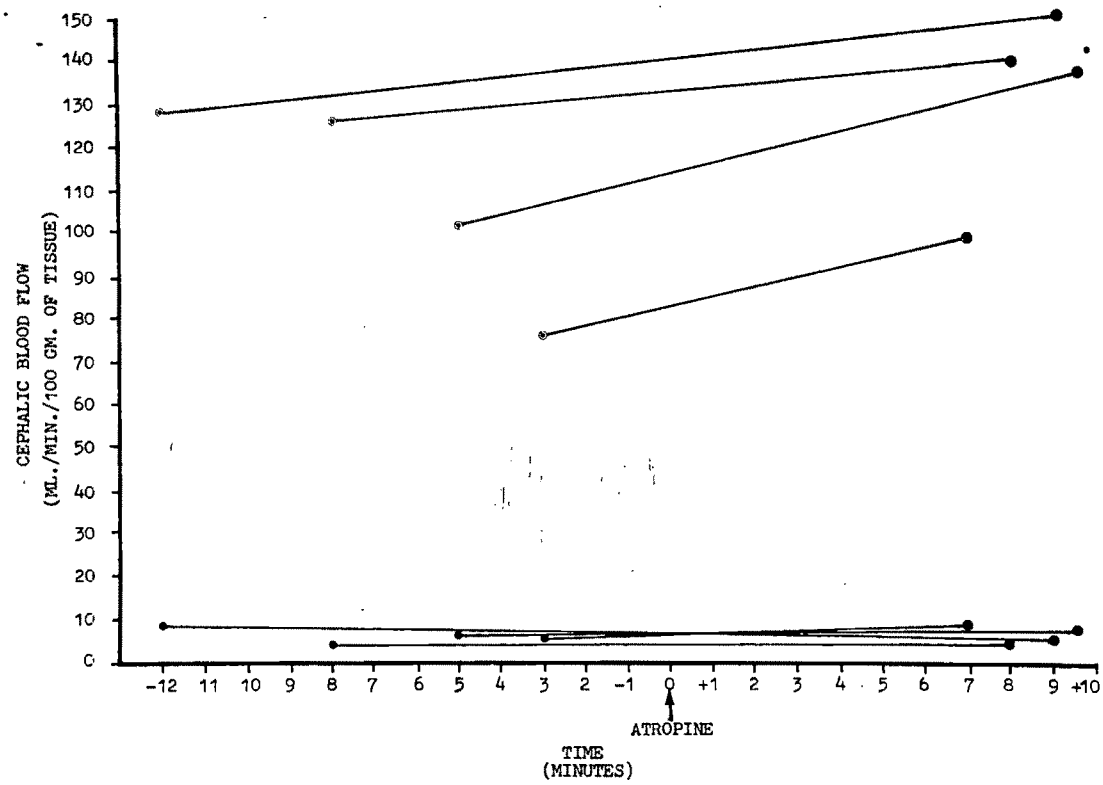


Fig. 4. Changes in cephalic blood flow before and after atropine. Small dot in white circle = cerebral blood flow; larger black dot = extracerebral blood flow.

further change. In our study the fetal weight varied from 1,470 to 4,125 grams and the gestional age from 112 to 144 days, based on Barcroft's measurements. Looking at an increase of an averaged fetal heart rate after atropine injection, six animals showed an increase of heart rate after 0.15 mg. of atropine and two animals did not ($P < 0.05$) (paired t test); but when we looked at the maximum increase in the fetal heart rate after atropine injection, all of the eight fetuses showed an increase of heart rate from the control level. The increase in heart rate behaved in almost the same way as reported in the other articles,[1-3] except the two fetuses whose baseline heart rates were very low. It is interesting to note that the fetus of 112 days' gestation and 1,470 grams increased its heart rate from 108.5 b.p.m. control level, to 208.8 b.p.m., the maximum increase. The control heart rate of 108.5 b.p.m. is somewhat low in comparison with the other control heart rate levels; however, the postatropine maximum increase of the fetal heart rate was almost the same as in other animals. This evidence may indicate an already existing vagal cardiomoderator tone in the fetal lamb as early as 112 days of gestation, and it was released by 0.1 mg. per kilogram of atriopine administration. The same kind of response occurred in a 142 days', 3,565 grams, mature fetus in this series whose control heart rate was 107.0 b.p.m. and postatropine maximum heart rate was 228.0 b.p.m.

The perfusion pressure of all animals in our study showed a small increase after atropine administration. This increase varied from 0.9 to 11.8 mm. Hg and seemed to be greater in the term fetuses, but there was no statistical significance. Since we did not measure peripheral vascular resistance in any other area but the cephalic region, we do not know whether there are any particular areas in the fetal systemic circulation which increased vascular resistance leading to an increase in the perfusion pressure. From our limited four observations, there appears to be no change in the cephalic vascular resistance.

According to Nuwayhid and associates,[3] 0.2 to 0.3 mg. per kilogram of intravenous atropine administration did not cause any significant change in the resting fetal aortic pressure in their chronic and acute fetal lamb preparations. On the other hand, the stimulation of afferent vagal pathways with Bezold-Jarish reflex (veratridine, 3 to 40 μg per kilogram) demonstrated a slight hypotension in the mature fetuses (>2,700 grams) and a significant increase in the immature fetuses (<1,500 grams). The fetuses between 1,600

and 2,600 grams showed either a slight increase or decrease in the arterial pressure, so that it is likely for the atropine to increase the fetal arterial pressure if the fetal vagal tone was already activated and vagal maturation has been achieved; but over all the pharmacologic effect on the fetal systemic circulation still remains to be elucidated.

Carotid blood flow was determined on six animals before and after the atropine. It revealed a small but statistically significant increase ($P < 0.05$) (paired t test).

Rudolph and Heymann[10] looked at the effect of the different levels of heart rate on the ventricular output by placing a magnetic flow meter around the pulmonary trunk of the fetal lamb. They increased the fetal heart rate by electric stimulation of left atrium with pulses of 2 msec. and voltage of 4 to 8 V. Right ventricular output rose as the heart rate was increased from 150 to 180 b.p.m. to 240 to 260 b.p.m. No further increase occurred to a rate of 285 to 315 b.p.m. With the rate above 300 to 325 b.p.m., there was a decrease in ventricular output. On the other hand, a slowing of the fetal heart rate by stimulation of the vagal nerve at a frequency of 15 per second with pulses of 2 to 3 msec., 5 to 25 V., was accompanied by a marked decrease of the right ventricular output. They also noted that parasympathetic blockade with atropine resulted in a variable small increase in heart rate and ventricular output. In Nuwayhid's observation on the fetal lamb[3] a very small, but not statistically significant, increase in blood flow in the mature fetuses occurred in both ascending aorta blood flow and ductus arteriosus flow after 0.2 to 0.3 mg. per kilogram of atropine was injected.

In the present study, blood flow was measured at one of the branches of the aortic arch and demonstrated a small but significant increase of carotid blood flow.

The response of the cephalic circulation in the four fetuses studied in the present series showed an appreciable increase in cerebral blood flow in each experiment, while there were no notable changes in the other cephalic parameters. Since there are no significant alterations in the blood flow/distribution, the cerebral blood flow increase may be related to the increased carotid blood flow and very low cerebral vascular resistance. It would be important to know whether there were any other critical peripheral vascular beds that were constricted by the atropine effect. If atropine does not constrict the placental and/or cardiac vascular beds, its action on the fetal circulation may not necessarily cause any deterimental effect in the dosage we have used.

Two animals at 128 days of gestation were subjected to a high carbon dioxided tension under the influence of atropine. Although one of these two fetuses showed an unexpectedly high carotid blood flow throughout the experiment, both of them showed appreciable responses to carbon dioxide administration. According to previous publications from our laboratory,[6, 8] the nonatropinized, semichronic fetal preparation increased its cerebral blood flow as the carbon dioxide tension was elevated. The extracerebral blood flow decreased reciprocally. The increase in cerebral blood flow of the nonatropinized fetus was 1.75 ml. per minute per 100 Gm. of brain for each millimeter of mercury increase of carbon dioxide. The decrease of the extracerebral blood flow was 0.45 ml. per minute per 100 Gm. of tissue. The present two atropinized animals showed very similar changes in cerebral blood flow to those of the nonatropinized fetuses. Their increases were 1.66 and 1.80 ml., respectively, whereas the decreases of the extracerebral blood flow were 0.4 and 0.1 ml. per minute per 100 Gm. of tissue in each millimeter of mercury increase of carbon dioxide. The cerebral and extracerebral vascular resistance of these

Table II. Physiologic data (atropinized fetuses) before and after CO_2 (S.E. of the mean)

	110S		*111S*	
Gest. age (days)	128		135	
pH	7.43 7.20		7.43 7.22	
Po_2	15.0 18.5		22.0 25.0	
Pco_2	52.0 84.0		46.0 75.0	
BE	+2.3 +2.1		+2.4 +2.6	
FHR (b.p.m.)	181.1 105.8	(5.5) (12.1)	201.5 161.3	(3.5) (7.5)
Perf. Pr. (mm. Hg)	54.9 59.1	(1.3) (0.9)	54.5 63.9	(0.6) (3.4)
Unilat. carotid flow (ml./min.)	116.8 114.3	(2.4) (4.5)	47.0 57.0	(1.1) (5.0)
Cerebral dist. (%)	73.8 87.3		84.3 93.2	
Extracereb. dist. (%)	26.2 12.7		15.7 6.8	
Cerebral flow (ml./min./100 Gm.)	337.6 390.6		153.5 205.8	
Extracereb. flow (ml./min./100 Gm.)	24.5 11.6		5.2 2.7	
Cereb. resist. (mm. Hg/ml./min./100 Gm.)	0.16 0.14		0.36 0.31	
Extracereb. res. (mm. HG/ml./min./100 Gm.)	2.23 5.04		10.58 23.67	

atropinized fetuses behaved in essentially the same way as in the nonatropinized fetuses.

These observations indicate that atropine is capable of increasing the cerebral blood flow. This is probably due to the increase in carotid blood flow caused by postatropine tachycardia. Elevation of carbon dioxide can also cause an increase in cerebral blood flow, adding to the effect of atropine.

Authors wish to express their appreciation to Nestor M. Budy and Patricia Jefferson for their technical assistance.

REFERENCES

1. Schifferli, P.-Y., and Caldeyro-Barcia, R.: *In* Boreus, L., editor: Fetal Pharmacology, New York, 1973, Raven Press, p. 259.
2. Vapaavouri, E. K., Shinebourne, E. A., Williams, R. L., Heymann, M. A., and Rudolph, A. M.: Neonate **22:** 177, 1973.
3. Nuwayhid, B., Brinkman, C. R., III, Su, C., Bevan, J. A., and Assali, N. S.: Am. J. Physiol. **228:** 337, 1975.
4. Mirkin, B. L.: *In* Boreus, L., editor: Fetal Pharmacology, New York, 1973, Raven Press, p. 1-27.
5. Bron, K. M., Murdaugh, H. V., Jr., Millen, J. E., Lenthall, R., Raskin, P., and Robin, E. D.: Science, **152:** 540, 1966.
6. Dunnihoo, D. R., and Quillgan, E. J.: AM. J. OBSTET. GYNECOL. **116:** 648, 1973.
7. Quilligan, E. J., Dunnihoo, D. R., and Anderson, G. G.: AM. J. OBSTET. GYNECOL. **109:** 706, 1971.
8. Dunnihoo, D. R.: Doctoral dissertation, University of Southern California, Los Angeles, Calif., 1972.
9. Boddy, K., Dawes, G. S., Fisher, R., Pinter, S., and Robinson, J. S.: J. Physiol. **243:** 599, 1974.
10. Rudolph, A. M., and Heymann, M. A.: Foetal and neonatal physiology, *in* Proceedings of the Sir Joseph Barcroft Centenary Symposium, London, 1973, Cambridge University Press, pp. 89-111.

In vitro perfusion of human placenta

V. Oxygen consumption

JEAN-CLAUDE CHALLIER, PH.D.
HENNING SCHNEIDER, M.D.
JOSEPH DANCIS, M.D.
New York, New York

O_2 consumption by human term placenta has been measured during perfusion in vitro, with a technique that permits perfusion of the intervillous space as well as the umbilical circulation. The rate at which O_2 was consumed was directly related to the rate at which it was supplied, within the limits studied. Previous estimates of O_2 consumption yielded figures approximating 3 ml. per minute per kilogram of placenta, but these estimates were attained under conditions of limited oxygen supply. When oxygen was delivered to the placenta at rates believed to be those achieved in vivo, oxygen consumption approximated 10 ml. per minute per kilogram. This rate of O_2 consumption is similar to those obtained from studies of animal placentas in vivo and is more consistent with that of an active metabolic organ. If one were to accept estimates of O_2 consumption by the human fetus in utero, the present studies indicate that approximately one fifth of maternal oxygen supplied to the conceptus is diverted to support placental metabolism.

THE PLACENTA is the major transport organ responsible for the delivery of nutrients from mother to fetus. It is also highly active metabolically, capable of synthesizing and degrading a wide variety of compounds. In vivo measurements of oxygen consumption of the placenta in several animal species have yielded figures consistent with such activity. However, attempts to estimate O_2 consumption of human placenta in vitro have produced results considerably lower, although human placenta is also known to be active metabolically.

O_2 consumption of human placenta has been reexamined with a technique capable of perfusing the intervillous space as well as the fetal circulation.

From the Departments of Obstetrics and Gynecology and of Pediatrics, New York University School of Medicine.

Aided by National Institutes of Health Grant no. HD00462.

Received for publication October 28, 1975.

Revised March 22, 1976.

Accepted April 9, 1976.

Reprint requests: Joseph Dancis, M.D., Department of Pediatrics, New York University Medical Center, 550 First Ave., New York, New York 10016.

Materials and methods

Perfusion technique. The technique has been described in detail previously.[1] Term placentas from normal vaginal or elective cesarian deliveries were carefully examined, a suitable cotyledon was selected, and perfusion of the tributary fetal vessels was initiated with Earle's buffered salt solution. The cotyledon was then isolated from the rest of the placenta and fixed in a perfusion device with the maternal surface facing upward. The area of the perfused tissue was clearly delineated on the decidual plate by its light color, which resulted from the washout of blood from the fetal capillaries. The decidual plate covering the intervillous space (IVS) over the perfused area was penetrated with two fine glass cannulas using gentle pressure and perfusion of the maternal conpartment was started. The time interval between delivery of the baby and the start of the perfusion ranged from 20 to 40 minutes. In those experiments in which only the IVS was perfused, the interval was reduced to 10 to 20 minutes.

The temperature of the preparation was carefully maintained at 37° C. The perfusate passed through an 8 ft. thin-walled stainless steel coil (I.D., 2.37 mm.; O.D., 2.77 mm.; Popper & Son, Inc.) in a 37° C. water

Table I. Placental O_2 consumption as measured by perfusion*

Compartment perfused	*No. of exps.*	*Perfusate*	*Gas mixture*	*Arterial Po_2 (mm. Hg)*	*ΔPo_2† (mm. Hg)*	*Arterial O_2 content (ml./100 ml.)*	*Flow* (ml./min./Kg.)*
Fetal	8	Earle	Air or 30% O_2 + 5% CO_2	161.4 ± 6.3	67.5 ± 5.8	0.54 ± 0.06	324 ± 84
Fetal	6	Earle	95% O_2 + 5% CO_2	548.7 ± 52.9	181.8 ± 10.4	1.84 ± 0.17	385 ± 79
Fetal (F) + maternal (M)	5	Earle	95% O_2 + 5% CO_2	F: 513.3 ± 42.2 M: 490.7 ± 30.8	162.8 ± 25.5 195.8 ± 27.9	1.72 ± 0.14 1.64 ± 0.10	431 ± 120 578 ± 197
Fetal	6	RBC‡ in Earle	Air or 30% O_2 + 5% CO_2	143.9 ± 5.0	73.4 ± 6.7	9.98 ± 0.39	111 ± 26
Fetal	2	Whole blood	Air + 5% CO_2	127.1 (112.8 – 141.5)	60.1 (59.5 – 60.8)	21 (20.6 – 21.4)	143 (88 – 97)
Fetal (F) + maternal (M)	6	RBC in Earle	Air or 30% O_2 + 5% CO_2	F: 150.4 ± 4.4 M: 154.8 ± 5.4	67.3 ± 5.7 76.6 ± 9.4	10.40 ± 0.26 10.37 ± 0.24	231 ± 80 253 ± 26
Maternal	5	Whole blood	Air + 5% CO_2	116.0 ± 6.2	43.7 ± 7.8	20.57 ± 0.41	794 ± 117

*Flow, O_2 supply, and O_2 consumption are listed as sum of maternal and fetal compartment for those experiments where both circuits were perfused. Results are means ± S.E.M. Range of results in parentheses.

†ΔPo_2 = arteriovenous difference in O_2 partial pressure.

‡RBC = washed red blood cells from fresh human blood suspended in Earle's buffered salt solution.

bath before entering the cotyledon which was housed in a plastic chamber in a 37° C. water bath. The entire perfusion apparatus was placed in a controlled-temperature chamber. Glass wool filters were placed in the circuit when blood was used as perfusate.

Perfusate. Earle's buffered salt solution with 100 mg. per 100 ml. glucose was used for the initial rinsing of fetal and maternal circuits and also as perfusion fluid in some of the experiments. The pH was adjusted to 7.35 with $NaHCO_3$.

Red blood cells (RBC) were obtained from fresh human blood obtained by phlebotomy from polycythemic patients. In some of the earlier experiments red cells of fresh defibrinated calf blood were used. The cells were separated from the plasma by centrifugation at 3,000 r.p.m. for 30 minutes at 4° C. Plasma was discarded and the cells were washed twice in twice the original volume of Earle's solution containing 30 mg. per 100 ml. of glucose and 3 mEq. of potassium and then suspended in Earle's solution with 3 mEq. of potassium and 5 Gm. per liter of low-molecular-weight dextran. The volume of the suspension fluid was adjusted to arrive at a final hematocrit of approximately 22 per cent. Before the experiment glucose was added in a concentration of 100 mg. per 100 ml. and the pH was adjusted to 7.35 at 37° C. with $NaHCO_3$ while the fluid was equilibrated with a gas mixture containing 5 per cent CO_2. Earle's solution with reduced potassium concentration was used to correct for the elevated potassium levels in the final perfusate, probably resulting from release of intracellular potassium from hemolysed red cells.

O_2 saturation curves were determined for the fresh washed human and calf red cells. The half-saturation Po_2 values ($Po_{2_{50}}$) were not significantly different from those recorded for adult fresh human whole blood. In contrast, red cells prepared from outdated human blood, i.e., 3 weeks or older, were found to have different O_2 saturation characteristics with a significant decrease in the $Po_{2_{50}}$ value. Outdated blood was not used in these studies.

Earle's solution and red cell suspensions were equilibrated against gas mixtures by continuous bubbling of the gas mixture through the reservoir containing the perfusate. Oxygenation of whole blood was performed in an evaporating flask of FE_2 Buchler Universal Flask evaporator, which was fixed in a horizontal position on a revolving shaft. A stream of air plus 5 per cent CO_2 saturated with water passed through the rotating flask which was partly immersed in a 37° C. water bath. The blood formed a thin layer covering the flask walls during rotation, permitting rapid equilibration with the gaseous phase without foaming. After full equilibration the blood was transferred into the perfusion reservoir and covered with a layer of paraffin oil.

Sampling and measurements. Samples were taken under airtight conditions with 3 c.c. disposable plastic syringes. Inflow and outflow of fetal and maternal compartments were sampled through three way Luer-lock stopcocks. In those experiments where high O_2 concentrations (95 per cent) were used, Po_2 and pH were measured immediately. In the remainder of the experiments the syringes were closed off by needles inserted into rubber stoppers and kept on ice until the

Wet weight of cotyledon	*O_2 supply (ml./min./Kg.)*	*O_2 consumption (ml./min./Kg.)*
36.0 ± 5.0	1.8 ± 0.5	0.7 ± 0.1
26.6 ± 3.6	7.6 ± 2.3	2.2 ± 0.3
27.3 ± 3.9	15.7 ± 3.0	5.3 ± 0.7
43.2 ± 3.6	11.2 ± 1.7	1.6 ± 0.3
49.5 (36 – 63)	29.7 (18.8 – 40.6)	3.1 (2.5 – 3.7)
37.6 ± 5.1	49.8 ± 8.7	3.3 ± 0.5
20.8 ± 2.1	164.7 ± 25.8	9.9 ± 1.8

measurements were performed at the end of the experiment.

Po_2 and pH were measured with a pH meter 22 from Radiometer. Hemoglobin content was determined with a Coulter counter model S and hemoglobin saturation with an oxymeter (American Optical Company). The perfusion flow was recorded by collecting the venous outflow over a timed interval.

The perfused cotyledon was excised from surrounding tissue at the end of the experiment, blotted, and weighed. In experiments with Earle's solution, the perfused part was easily identified by its light color. After perfusion with whole blood or suspensions of red cells the area corresponding to the fetal vascular compartment was visualized by injecting hydropaque dye (Comray, Mallindkrodt Pharmaceuticals) into the chorionic vessels. By superposition of an x-ray the perfused area could be outlined and then excised. For the experiments in which only the IVS was used for the perfusion with whole blood an anatomically well-delineated cotyledon was selected on the maternal surface of the placenta. The perfused area was easily recognized at the end of the experiment by its dark color as well as the slight elevation of the maternal surface over the surrounding nonperfused cotyledons. This area was excised, blotted, and weighed.

Calculations. Oxygen consumption was calculated from arteriovenous difference in O_2 content, flow-rate, and net weight of the cotyledon according to the equation

$$\frac{O_2 \text{ consumption}}{(\text{ml./min./Kg.})} = \frac{\Delta O_2}{100} \times Q \times \frac{1{,}000}{C} \qquad (1)$$

where ΔO_2 = arteriovenous difference in O_2 content in milliliters per 100 ml. of perfusate, Q = perfusion flow in milliliters per minute and C = wet weight of cotyledon in grams.

Oxygen content was calculated for perfusates with physically dissolved oxygen and whole blood or red cell suspensions by Eqs. 2 and 3, respectively.

$$\frac{O_2 \text{ content}}{(\text{ml./100 ml.})} = \frac{Po_2 \times \alpha \times 100}{P_B - P_{H_2O}} \qquad (2)$$

$$\frac{O_2 \text{ content}}{(\text{ml./100 ml.})} = \left[\begin{matrix}\%\text{ sat.} \times \\ \text{Hb} \times \text{H}\end{matrix}\right] + \left[\frac{Po_2 \times \alpha \times 100}{P_B - P_{H_2O}}\right] \qquad (3)$$

where Po_2 = O_2 partial pressure in millimeters of mercury, α = solubility coefficient of O_2 in milliliters per milliliter of perfusate, P_B = barometric pressure in millimeters of mercury, P_{H_2O} = water vapor pressure at 37° C. in millimeters of mercury, % sat. = per cent O_2 saturation of hemoglobin, Hb = hemoglobin concentration in grams per 100 ml., and H = Huffner coefficient.

For Earle's solution an α of 0.0239 was used which was originally determined for Ringer's solution[2]; the α for blood was calculated according to the formula of Sendroy.[3]

Oxygen supply, which is defined as the amount of oxygen perfused per minute per kilogram of tissue was calculated from Eq. 1 by replacing ΔO_2 by arterial oxygen content.

Results

With buffered salt solutions as perfusate, O_2 consumption bore a direct relation to the rate with which O_2 was supplied (Table I, Fig. 1). Maximal O_2 delivery with this system (15.7 ml. per minute per kilogram of placenta) was achieved by equilibrating the buffer solution with 95 per cent O_2 + 5 per cent CO_2 and by circulating it through both the maternal and fetal compartments at high perfusion flow rates (total of IVS and villous capillary flow of 1,000 ml. per minute per kilogram). Under these conditions O_2 consumption was 5.3 ml. per minute per kilogram.

The use of RBC, either suspended in buffer or as whole blood, greatly increased the rate at which O_2 could be delivered to the placenta. There was again a direct relation between the rate of O_2 delivery and O_2 consumption (Fig. 2). In this series of experiments, maximal O_2 delivery was achieved by perfusion of the IVS with whole blood at a high flow rate (Table I). In four experiments with high oxygen delivery, the O_2 consumption was 7.29, 7.99, 14.03, and 14.44 ml. per minute per kilogram of placenta, with a mean of 10.9.

Comment

Measurements of O_2 consumption by human placenta in vivo are currently impossible because of technical and ethical constraints. In vitro measurements have been made by several investigators, with results that appear too low to support the

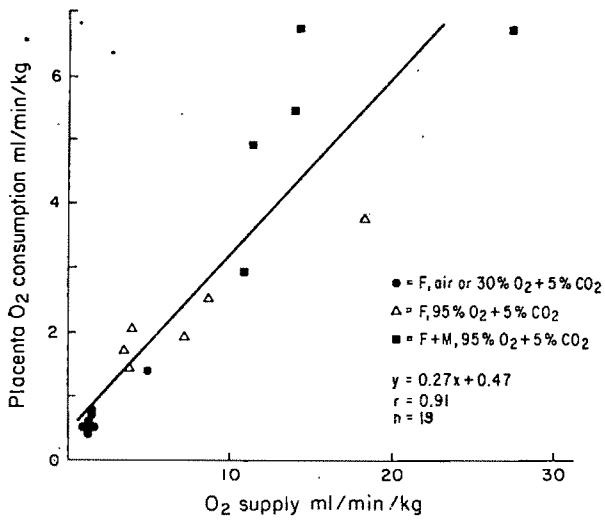


Fig. 1. Oxygen consumption of human placenta. Oxygen was delivered physically dissolved in buffered salt solution through the fetal circulation *(F)* or fetal and maternal circulations *(F + M)*.

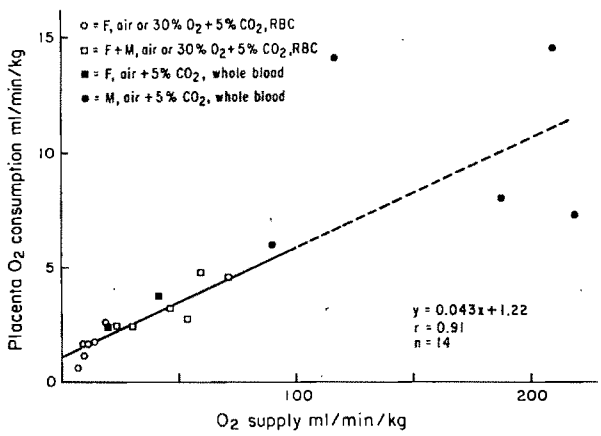


Fig. 2. Oxygen consumption of human placenta. Oxygen was delivered following equilibration of hemoglobin-containing perfusate with gas mixture. RBC, washed red blood cells suspended in buffer. *F*, Fetal circulation; M, maternal circulation.

metabolic activities attributed to the placenta. Oxygen consumption of human placental slices incubated in buffered salt solution equilibrated with 95 per cent O_2 has yielded figures of 2.92 to 4.83 ml. per minute per kilogram of wet weight.[4–6] (These figures were obtained after conversion of dry weight into wet weight with a tissue water content of 87.5 per cent.[4]) Perfusion studies have provided similar estimates. Budelman[7] reported an oxygen consumption rate of 3.0 ml. per minute per kilogram of placenta when the fetal circulation of human placenta was perfused with defibrinated dog blood; Nyberg and Westin,[8] using the same technique with fresh human blood, reported 3.7 ml. per minute per kilogram of placenta.

The development of a technique capable of perfusing the intervillous space as well as the umbilical circulation encouraged us to reinvestigate the question. The initial studies were done with buffered salt solution equilibrated with 95 per cent O_2–5 per cent CO_2. A clear correlation of rate of O_2 delivery to the placenta with O_2 consumption was obtained (Fig. 1). With high flow rates achieved by perfusing both the intervillous space and the umbilical circulation, a maximal oxygen consumption of 5.3 ml. per minute per kilogram was achieved.

The use of hemoglobin-containing solutions, either RBC suspended in buffer or whole blood, greatly increased the rate at which O_2 could be delivered to the placenta even though the solution was equilibrated with air or 30 per cent O_2 rather than with 95 per cent O_2. Perfusion of only the umbilical circulation with hemoglobin-containing solutions provided a figure for oxygen consumption of 3.7 ml. per minute per kilogram, very close to that obtained by previous investigators using the same technique.[7, 8] These low results appeared to result directly from the limitations in oxygen delivery due to limited flow. With whole blood, flow rates of only 90 to 197 ml. per kilogram of placenta could be achieved in the fetal circulation without excessively raising the pressure in the circuit. This is significantly below estimated in vivo flows.

Perfusing the IVS made possible an increased rate of O_2 delivery because a reduced resistance permitted high flow rates even with more viscous solutions such as blood. This route had the additional advantage of directly exposing the metabolically active syncytiotrophoblast to the perfusate, reproducing more closely the physiologic situation.

Anatomically, the intervillous space is continuous throughout the placenta, but at high flow rates there is a relative confinement of the perfusate to the cotyledon. Injection of radiopaque dye into the IVS through the spiral arteriole has demonstrated a spurt into the center of the cotyledon with slow drainage through venous sinuses in the basal plate. The spillover into neighboring cotyledons was relatively minor.[9] Our experience confirms this interpretation. During perfusion of the IVS of the isolated cotyledon the basal plate lifts up slightly, indicating an increase in pressure as a result of relative confinement of entering perfusate, with escape of the fluid through three or four venous openings in the plate. The perfused area, as identified by this slight swelling and the changes in color induced by the perfusate, was excised at the end of the experiment and weighed.

A direct relation between O_2 delivery and O_2 con-

sumption was demonstrated for red cell–containing perfusates and whole blood with a lower slope (reduced efficiency) of O_2 utilization than for Earle's solution (Figs. 1 and 2). The efficiency of utilization defined as the ratio of O_2 consumption to O_2 supply was less than with buffered salt solutions even when Po_2 was maintained constant. When Earle's buffered salt solution was equilibrated with air, 29 to 41 per cent of the delivered oxygen was consumed. With washed red cells or fresh human whole blood similarly equilibrated, only 6 to 14 per cent of delivered O_2 was consumed. It would appear, that under the conditions of these studies the rate of release of O_2 from hemoglobin and diffusion from the red blood cell might have limited the available O_2.

Similar observations concerning the relation between O_2 delivery and O_2 consumption have been reported for O_2 consumption of tumor studied by perfusion techniques.[10] O_2 consumption was directly proportional to the amount delivered to the tumor over a wide range. No plateau was observed. Because of hemodynamic problems, the maximal O_2 delivery was slightly below that achieved in vivo. The question of saturation at higher rates of O_2 supply remains unanswered.

Most of our experiments explored the relationship between O_2 supply and consumption at rates of O_2 delivery of 100 ml. per minute per kilogram of placenta or less. However, estimates of O_2 supply to the placenta in vivo are considerably higher. If one were to assume a blood flow of 500 ml. per minute throughout the IVS of a term placenta of 500 grams, an arterial Po_2 of 98 mm. Hg, a hemoglobin content of 12 Gm. per 100 ml., and a hemoglobin O_2 saturation of 97 per cent, the O_2 supply to the placenta would approximate 160 ml. per minute per kilogram of placenta. Extrapolation of the relation of O_2 supply to O_2 consumption as presented in Fig. 2 yields an estimate for O_2 consumption in vivo of about 8.5 ml. per minute per kilogram.

Only four experiments were performed that fell within this high range of O_2 delivery. The results were 7.27, 7.99, 14.03, and 14.44 ml. per minute per kilogram of placenta, with a mean of 10.9. Both the observed and the calculated rates of O_2 consumption by human placenta determined in these studies are very similar to the estimates for sheep and rabbit placenta (10.4 and 10.7 ml. per minute per kilogram) made from measurements in vivo.[11, 12] The rate of O_2 consumption by human placenta derived from these studies is considerably higher than suggested by previous studies, and is more appropriate for an organ known to be so active metabolically.

Insofar as the delivery of O_2 to the fetus is a primary function of the placenta, the magnitude of diversion of maternal O_2 to placental metabolic activity is of interest. The rates of O_2 consumption in the placenta and fetus in the rabbit are 10.4 and 6.0 ml. per minute per kilogram, respectively. Similar figures have been obtained in the pregnant sheep (10.4 and 6.0 ml. per minute per kilogram, respectively). If one were to accept Bartels'[14] figure for O_2 consumption by the human fetus, the ratio of placental vs. fetal O_2 consumption in the human would be approximately 10.9 ml. per minute per kilogram to 7.4. Assuming fetal and placental weights of 3.5 and 0.5 kilogram, respectively, at term approximately 17 per cent of the maternal O_2 supply to the conceptus is pre-empted by the metabolic activities of the placenta.

REFERENCES

1. Schneider, H., Panigel, M., and Dancis, J.: Transfer across the perfused human placenta of antipyrine, sodium and leucine, Am. J. Obstet. Gynecol. **114:** 822, 1972.
2. Dixon, M.: Manometric Methods, ed. 2, Cambridge, England, 1943, Cambridge University Press.
3. Sendroy, J., Jr., Dillon, R. T., and Van Slyke, D. D.: Studies of gas and electrolyte equilibria in blood. XIX. The solubility and physical state of uncombined oxygen in blood, J. Biol. Chem., **105:** 597, 1934.
4. Villee, C. A.: Metabolism of human placenta in vitro. J. Biol. Chem. **205:** 113, 1953.
5. MacKay, R. B.: Studies of the oxygen consumption of fresh placental tissue from normal and abnormal pregnancies, J. Obstet. Gynaecol. Br. Emp. **65:** 791, 1958.
6. Friedman, E. A., and Sachtleben, M. R.: Placental oxygen consumption in vitro. I. Baseline studies, Am. J. Obstet. Gynecol. **79:** 1058, 1960.
7. Budelman, G.: Einiges uber Stoffwechsel und Gefassreaktionen der uberlebenden, menschlichen Placenta, Z. Gesamte Exp. Med. **67:** 731, 1929.
8. Nyberg, R., and Westin, B.: The influence of oxygen tension and some drugs on human placental vessels, Acta Physiol. Scand. **39:** 216, 1957.
9. Panigel, M.: Morphological evaluation of perfused tissues, *in* Diczfalusy, E., editor: Karolinska Symposium on Research Methods in Reproductive Endocrinology: 4th symposium, Perfusion Techniques, New York, 1971.
10. Gullino, P. M.: In vitro perfusion of tumors, *in* Norman, J. C., editor: Organ Perfusion and Preservation, New York, 1968, Appleton-Century-Crofts.
11. Campbell, A. G. M., Dawes, G. S., Fishman, A. P., Hyman, A. I., and James, G. B.: The oxygen consumption of the placenta and foetal membranes in the sheep, J. Physiol. (Lond.) **182:** 439, 1966.
12. Faber, J. J., and Hart, F. M.: The rabbit placenta as an organ of diffusional exchange. Comparison with other species by dimensional analysis, Circ. Res. **19:** 816, 1966.
13. James, E. J., Raye, J. R., Gresham, E. L., Makowski, E. L., Meschia, G., and Battaglia, F. C.: Fetal oxygen consumption, carbon dioxide production, and glucose uptake in a chronic sheep preparation, Pediatrics **50:** 361, 1972.
14. Bartels, H.: Prenatal respiration, *in* Frontiers of Biology, vol. 17, Amsterdam/London, 1970, North-Holland Publishing Company.

The significance of fetal electrocardiography in the diagnosis of intrauterine bradyarrhythmia

E. G. ABINADER, M.D.
A. KLEIN, M.D.
I. EIBSCHITZ, M.D.
A. ZILBERMAN, M.D.
B. PEZESHK, M.D.
M. SHARF, M.D.
Haifa, Israel

From 11 cases of fetal bradycardia diagnosed by monitoring of 130 fetal electrocardiograms (ECG's) in high-risk pregnancies we have presented our experience in three selected cases of fetal bradyarrthythmia. Case 1 revealed on ECG blocked atrial premature beats simulating an extreme sinus bradycardia sequentially followed by conducted atrial premature beats. In case 2 we diagnosed ventricular premature beats in the form of persistent bigeminy which was controlled by intravenous propranolol. The last case illustrated the phenomenon of aberrant ventricular conduction known to occur in adult cardiology. The electrophysiologic basis of the variable arrhythmias was discussed. Detailed analysis of repeated direct fetal ECG's provided us with the diagnosis and understanding of the electrophysiologic mechanisms underlying the rhythm disturbances. This consequently determined the pharmacologic therapy and the obstetric approach relevant to each case. We have shown that by direct fetal electrocardiography it is possible to analyze accurately the rhythm disturbances. Persistent fetal bradycardia does not always signify fetal distress. We hope that this study will lead to closer teamwork between the obstetrician and the cardiologist which will give an impetus to the future development of "fetal cardiology," thereby enhancing our understanding of the electrophysiology of the fetal heart.

WORTHWHILE contributions have been provided by direct fetal ECG's in the diagnosis and management of fetal rhythm disturbances.[1, 2] Persistent fetal bradycardia during labor is considered to be an ominous sign of fetal distress and invariably calls for urgent obstetric intervention.

We wish to present our experience in three selected cases of fetal bradyarrhythmias in which accurate analysis of the direct fetal ECG provided us with the understanding of the electrophysiologic mechanism of the arrhythmia which consequently determined the mode of pharmacologic therapy and the obstetric approach.

From the Department of Obstetrics and Gynecology and the Cardiologic Unit, Rothschild University Hospital, Aba Khoushy School of Medicine.

Received for publication December 30, 1975.

Accepted March 31, 1976.

Reprint requests: E. G. Abinader, M.D., Cardiologic Unit, Rothschild University Hospital, The Aba Khoushy School of Medicine, P.O. Box 4940, Haifa, Israel.

Material and method

In all cases of high-risk pregnancies, chronic placental insufficiency, and acute fetal distress, constant external cardiotocographic monitoring was performed from the onset of labor. As soon as rupture of membranes occurred, a direct fetal ECG was performed simultaneously with external registration of uterine contractions.

Continuous monitoring was recorded with Hewlett-Packard 8020A cardiotocograph in conjunction with a 15180A ultrasound amplifier and a 15139A display unit connected to a 1500A ECG. Fetal blood samples for acid-base balance were collected into polyvinyl tubes with the instruments and technique described by Saling.[3] The samples were immediately examined in an Astrup apparatus with the use of the Siggaard-

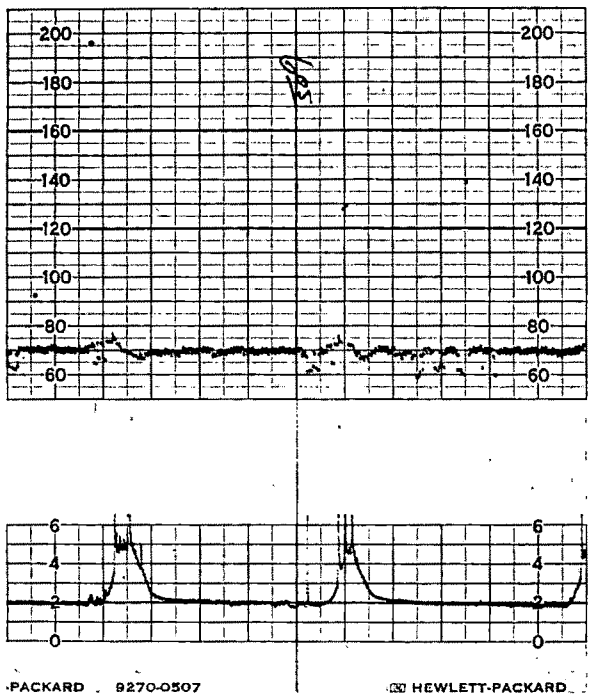


Fig. 1. Cardiotocogram showing persistent fetal bradycardia unrelated to uterine contractions.

Andersen nomogram.[4] All ECG records were taken at paper speed of 25 mm. per second and sensitivity 1, unless indicated otherwise. Cardiotocogram records were taken at paper speed of 1 cm. per minute.

Of 130 monitored cases, 11 cases of fetal bradycardia were diagnosed. Of these we selected the following illustrative cases pertinent to our discussion.

Case reports

Case 1. L. N., a 28-year-old woman, gravida 3, para 2, was admitted to our delivery room with postdate pregnancy of 8 days and uterine contractions during the preceding 4 hours. On admission a fetal heart rate of 65 to 70 beats per minute was noted, the cervix was effaced and dilated to 4 cm. and the head was at −1 station. The membranes were ruptured artifically and the amniotic fluid was clear. Direct fetal ECG by scalp electrode was immediately registered and a fetal heart rate of 64 per minute was documented. Simultaneous external monitoring of uterine contractions failed to demonstrate a causal relationship between the bradycardia and the uterine contractions (Fig. 1). The direct fetal ECG revealed blocked atrial premature beats (Fig. 2, *A*) with occasional episodes of conducted atrial premature beats in the form of bigeminy (Fig. 2, *B*). Fetal acid-base balance revealed: pH, 7.28; P_{CO_2}, 56.5 mm. Hg; base excess, 8.4 mEq. per liter; standard bicarbonate, 17.7 mEq. per liter. These values were within normal limits. Labor was terminated in normal

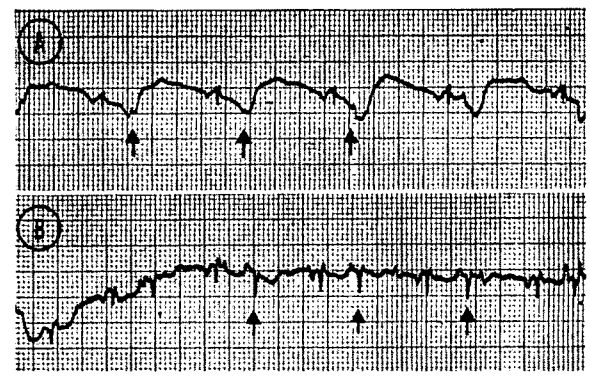


Fig. 2. Direct fetal ECG revealing *(A)* blocked atrial premature beats, marked by arrows, simulating sinus bradycardia, and *(B)* conducted atrial premature beats in the form of bigeminy, marked by arrows.

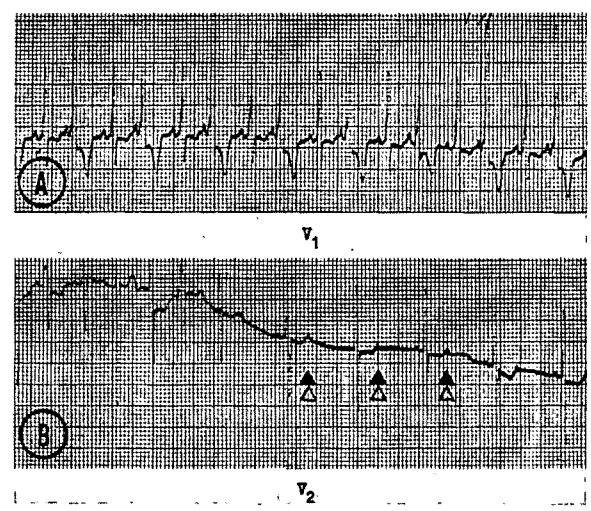


Fig. 3. Leads V_1 and V_2 of the neonatal ECG demonstrating *(A)* atrial bigeminy and *(B)* continuous strip of Lead V_2 showing atrial bigeminy followed by blocked atrial premature beats (see arrows).

vaginal delivery 3 hours later. A 12 lead ECG done in the newborn infant revealed episodes of atrial bigeminy (Fig. 3). Repeat 12 lead ECG revealed reversion to normal sinus rhythm 1 week after birth. Following examinations revealed no cardiac pathology.

Case 2. D. L., a 25-year-old woman, gravida 2, para 1, was monitored from the onset of labor by external cardiotocogram because of gestional diabetes. Fetal bradycardia was noted during the active stage of labor (Fig. 4, *A*), at which time the uterine cervix was dilated to 5 cm. Fetal membranes were ruptured in order to register a direct fetal ECG with a scalp electrode; clear amniotic fluid was observed. Fetal ventricular premature beats in the form of persistent bigeminy was recorded (Fig. 4, *B*). Maternal ECG taken simultaneously with fetal electrocardiogram was normal. Fetal

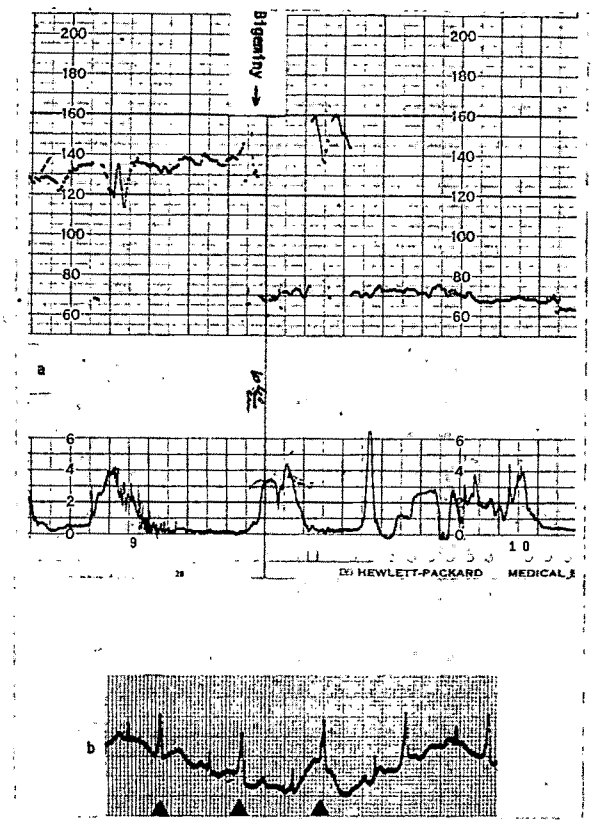


Fig. 4. *(A)* Cardiotocogram showing bradycardia caused by the onset of ventricular bigeminy which was unrelated to uterine contractions. *(B)* Direct fetal ECG during the bradycardiac period showing in *(A)* with arrows pointing to the ventricular premature beats.

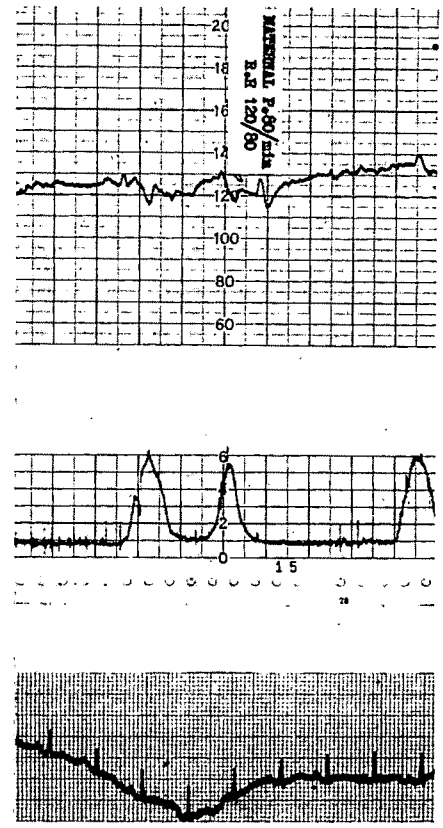


Fig. 5. Cardiotocogram and direct fetal ECG after reversion to sinus rhythm following intravenous propranolol.

acid base balance was within normal limits; pH, 7.30; P_{CO_2}, 30 mm. Hg; base excess, 10 mEq. per liter; standard bicarbonate, 14.75 mEq. per liter. In view of the persistence of the fetal ventricular arrhythmia we administered 6 mg. of propranolol intravenously to the mother at the rate of 1 mg. per minute.[5] The arrhythmia disappeared within minutes (Fig. 5). Labor ended in normal vaginal delivery with no maternal or fetal side effects. Immediate examination of the newborn infant, including a 12 lead ECG and a repeat examination the next half year, revealed no pathology.

Case 3. S. O., a 26-year-old woman, gravida 1, para 0, was admitted at term with rupture of membranes. Examination revealed an 80 per cent effaced cervix dilated to 1.5 cm. Regular uterine contractions, 2 to 3 every 10 minutes, were registered. At this stage fetal cardiac irregularity was noted. Consequently, phonocardiogram and direct fetal ECG were recorded. Fetal acid-base balance performed was within normal limits; pH, 7.25; P_{CO_2}, 38 mm. Hg; base excess, 10 mEq. per liter; standard bicarbonate, 16.0 mEq. per liter. The phonocardiogram revealed a persistent trigeminy (Fig. 6, *A*) which was shown to be of atrial

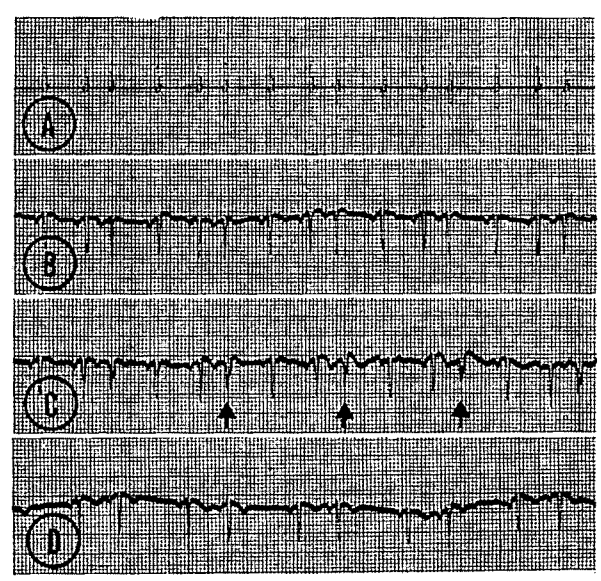


Fig. 6. *(A)* Phonocardiogram revealing an arrhythmia in the form of trigeminy. *(B)* Direct fetal ECG revealing the atrial origin of the trigeminy. *(C)* Sequential but noncontinuous tracing of same fetus showing atrial premature beats conducted to ventricles with aberration (see arrows.) *(D)* Sequential tracing showing blocked atrial trigeminy.

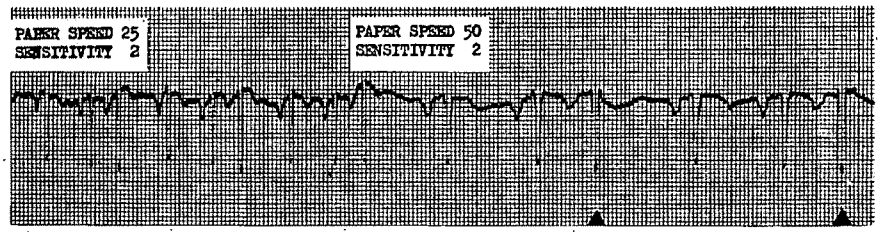


Fig. 7. Direct fetal ECG registered at twice the sensitivity and paper speed for better demonstration of the atrial trigeminy (see arrows). The ectopic P waves are clearly seen deforming the preceding T waves.

origin in the ECG (Fig. 6, *B*). These atrial premature beats were occasionally conducted to the ventricles with aberration, as shown in Fig. 6, *C*, and at times the atrial premature beats were completely blocked (Fig. 6, *D*). Fig. 7 demonstrates the fetal ECG taken at twice the normal sensitivity with the latter half of the trace at at 50 mm. second. The atrial trigeminy is obvious. The mother received 50 mg. of pethidine together with 25 mg. of phenergan, which was followed by fetal sinus rhythm without ectopic activity. The progress of labor was satisfactory and ended 7 hours later in normal vaginal delivery. A 12 lead ECG registered in the newborn infant revealed a normal neonatal pattern without arrhythmia. There was no evidence of congenital heart disease.

Comment

Although great advances were made in the analysis of complex rhythm disturbances in the adult, minor progress, relatively speaking, has been achieved to date in the analysis and understanding of fetal rhythm disturbances.[6]

We have presented three selected cases in which detailed analysis of the direct fetal ECG accurately determined the variable nature of the rhythm disturbance thus modifying the pharmacologic and obstetric approach.

In the first case persistent fetal bradycardia was recorded by cardiotocograph (Fig. 1). It is obvious from the record that there was no causal relationship between the uterine contractions and the fetal bradycardia.

Initial examination of the fetal trace (Fig. 2, *A*) may erroneously lead to the diagnosis of fetal sinus bradycardia of 64 beats per minute. However, detailed and accurate analysis of this and subsequent tracings (Fig. 2, *A*) clearly reveals episodes of blocked atrial bigeminy as shown by the deformities in the preceding T waves caused by the blocked atrial premature beats. This was confirmed in Fig. 2, *B*, in which the atrial premature beats occured later and therefore were conducted to the ventricles as they fell outside the refractory period of the junctional tissues. Simultaneously, acid-base balance results excluded fetal distress and confirmed the diagnosis of the rhythm disturbance as the basis of the fetal bradycardia. A 12 lead ECG done in the newborn infant confirmed the above diagnosis. In Lead V_2 of Fig. 3, continuous trace demonstrates conducted atrial bigeminy followed by blocked atrial premature beats also in the form of bigeminy.

Another form of bigeminy is that due to ventricular premature beats appearing after each normally conducted sinus beat. This was diagnosed in our second case. In comparison to the atrial bigeminy recorded in the first patient, the premature beats were not preceded by a P wave and the QRS complex was widened above 0.04 to 0.05 second, which is the upper normal limit of a normal fetal QRS complex (Fig. 4). There was in addition a full compensatory pause after the premature beat. All these criteria point to the ventricular origin of such beats. In view of the persistence of the ventricular bigeminy, the detrimental hemodynamic consequence, and the possibility of the triggering of ventricular tachycardia,[5] we administered to the mother intravenous propranolol which terminated the rhythm disturbance within minutes (Fig. 5) without untoward maternal or fetal side effects. This successful outcome is in accord with our previous experience in a similar arrhythmia which was successfully reverted to sinus rhythm following intravenous propranolol.[5] The phenomenon of FHR trace which does not reflect the arrhythmia is due to the "logic" limitation of the cardiotocograph that no rate higher than 210 beats per minute or changes of more than 30 beats per minute are counted. This phenomenon should be remembered by the clinician in order to avoid a diagnostic error.

The increased width of the QRS complex does not always point to the ventricular origin of the premature beats, as we have demonstrated in the last case. The trigeminy noted on phonocardiography (Fig. 6, *A*) was proved to be due to atrial premature beats (Fig. 6, *B*) as these beats were preceded by premature ectopic P waves deforming T waves of the normally conducted

sinus beat and the postectopic pauses were not fully compensatory.

However, in the same fetus we observed premature beats with wide QRS complexes of 0.07 to 0.08 second (Fig. 6, *C*). At first look, these beats simulate ventricular premature beats but detailed analysis of these premature beats points to their supraventricular origin. They were all preceded by an ectopic P wave which appeared earlier than those seen in Fig. 6, *B* and deforming the T wave of the normal sinus beat. Those beats were not followed by a full compensatory pause, which further points to their atrial origin. The electrophysiologic explanation for the widened QRS complex lies in the fact that the earlier appearance of the premature atrial beat arrives at the atrioventricular conduction system before their full recovery and hence are conducted to the ventricles with aberration leading to a widened QRS complex. Sequential but noncontinuous records shown in Fig. 6, *D* of the same fetus demonstrate blocked atrial premature beats. These beats occurred even earlier, reaching the junctional tissues while the latter were still completely refractory, hence preventing further propagation of the impulse to the ventricles. ECG registration at twice the speed and sensitivity may help in the diagnosis of these rhythm disturbances, as seen in Fig. 7.

It is obvious from our accumulated experience in the study of rhythm disturbances in the fetus that persistent fetal bradycardia does not always signify fetal distress.

Acid-base balance monitoring is imperative for establishing fetal distress. Even a direct fetal ECG may at times be misleading in the diagnosis of extreme fetal bradycardia of sinus origin unless detailed and accurate analysis is performed, particularly to evaluate the presence of blocked atrial premature beats. Furthermore, a widened QRS complex of an ectopic beat in the fetus, as in the adult, does not always point to a ventricular origin but may be due to aberrant conduction. We wish to stress the fact that detailed analysis of fetal rhythm disturbances would minimize unnecessary drastic obstetric interventions.

The detailed fetal ECG analysis which should develop further in the future will undoubtedly determine in certain cases the therapeutic approach both pharmacologically and obstetrically.

We hope that our experience presented in this manuscript will encourage the development of closer teamwork between the obstetrician and the cardiologist during pregnancy and at labor. We envisage in the near future further development in the field of "fetal cardiology" which would enhance our understanding of the electrophysiology of the fetal heart.

REFERENCES

1. Takemura, H.: Studies on fetal ECG informations in late pregnancy and parturition. Part II. The FECG configurations and fetal arrhythmias, J. Jap. Obstet. Gynecol. Soc. **13:** 30, 1966.
2. Teteris, N. J., Chisholm, J. W., and Ullery, J. C.: Antenatal diagnosis of congenital heart block, Obstet. Gynecol. **32:** 852, 1968.
3. Saling, E.: Some experiences on more than two thousand foetuses being followed by amnioscopy and microblood examination, *in* Horsky, J., and Stembera, Z. K., Editors: International Symposium on Intrauterine Dangers to the Foetus, Prague, 1966, Amsterdam, 1967, Excerpta Medica Foundation, p. 318.
4. Astrup, P., Jorgensen, K., Siggaard-Andersen, O., and Engel, K.: The acid-base metabolism. A new approach, Lancet **1:** 1035, 1960.
5. Eibscitz, I., Abinader, E. G., Klein, A., and Sharf, M.: Intrauterine diagnosis and control of fetal ventricular arrhythmia during labor, Am. J. Obstet. Gynecol. **122:** 597, 1975.
6. Shenker, L.: Fetal electrocardiography, Obstet. Gynecol. Surv. **21:** 367, 1966.

Moderate fetal bradycardia

BRUCE K. YOUNG, M.D., F.A.C.O.G.*
HOWARD M. WEINSTEIN, M.D.
New York, New York

Fetal heart rates in the range of 100 to 119 beats per minute have been defined as moderate bradycardia. Twenty-five of 1,386 patients monitored during a 1 year period have manifested persistent moderate bradycardia. Moderate bradycardia is apparently related to fetal head compression, often in situations of relative cephalopelvic disproportion. It is alleviated by rotation of the vertex and does not appear to adversely affect the newborn infant.

MODERATE bradycardia of the fetal heart is defined as being in the range of 100 to 119 beats per minute (b.p.m.) and is rarely associated with depressed newborn infants unless accompanied by marked periodic decelerations in the fetal heart rate (FHR).[1] Prolonged bradycardia as an isolated finding has been observed with congenital heart lesions.[2] This study describes a clinical association between persistent moderate bradycardia of the fetal heart and fetal head compression during labor.

Materials and methods

This study was performed at the Bellevue Hospital Center during the period from July 1, 1974, to June 30, 1975. There were 1,386 continuously monitored labors during this time period. During this time there were 25 patients continuously monitored who manifested moderate bradycardia in labor. Length of labor in these patients varied from 2 hours and 25 minutes to 14 hours and 11 minutes, with a mean duration of 7 hours and 36 minutes. Corometrics 101B† and Roche Fetasonde 2101‡ fetal monitors were utilized for direct internal monitoring with spiral scalp electrodes during this period. All records were reviewed by the same investigators.

From the Department of Obstetrics and Gynecology, New York University School of Medicine, Bellevue Hospital Center.

Received for publication October 30, 1975.

Revised March 23, 1976.

Accepted April 9, 1976.

Reprint requests: Bruce K. Young, M.D., Department of Obstetrics and Gynecology, New York University Medical Center, 550 First Ave., New York, New York 10016.

**Irma T. Hirschl Career Scientist.*

†Corometrics Medical System, Inc., Wallingford, Connecticut.

‡Roche Medical Electronics Division, Hoffmann-La Roche, Inc., Cranbury, New Jersey.

Results

Moderate bradycardia was observed in 1.8 per cent of all patients monitored in labor. Table I summarizes the clinical data for the 25 patients studied. There were 17 primigravidas and eight multiparas in this series. In all cases, the baseline fetal heart rate was within the normal range of 120 to 160 b.p.m. prior to the onset of the persistent bradycardia. All patients had ruptured membranes.

The fetal heart rate during the episode of persistent bradycardia ranged from 100 to 119 b.p.m., excluding periodic changes (Fig. 1). The mean duration of the episode of bradycardia was 51 minutes. No change in baseline variability was noted during the bradycardic episode and no abnormality in fetal electrocardiogram was observed.

During the episode of bradycardia, frequent vaginal examinations revealed significant clinical events concerning the position of the fetal vertex. All cases, except a persistent brow presentation, were associated with a significant change in the position of the vertex from posterior or transverse to transverse or anterior (Fig. 2). Neither administration of oxygen to the mother nor change in her position alleviated the bradycardia. Only meperidine and promethazine combinations were used for analgesia for these patients, and did not induce or influence the bradycardia. Only rotation of the vertex appeared to influence recovery of the fetal heart rate to "normal" levels.

No particular association was noted between the episode of bradycardia and a specific FHR change, although nine patients did manifest early decelerations

Table I. Summary of patients manifesting persistent moderate bradycardia during labor

Pt.	*Parity*	*Baseline FHR range (b.p.m.)*	*FHR during bradycardia episode (b.p.m.)*	*Length of bradycardia (min.)*	*Clinical events (rotation)*	
					From	*To*
M. A.*	0	130-140	110-115	180	OP†	ROT†
E. T.	0	120-140	110-115	85	LOT	LOA
J. S.	0	130-160	100-110	25	LOP	LOT
M. M.	0	120-140	110-115	8	LOT	LOA
L. D.	0	120-140	105-115	60	OP	LOT
M. G.*	1	120-140	100-110	45	LOP	LOA
C. R.	1	130-140	105-110	110	LOP	LOA
D. W.	0	130-150	110-115	35	ROP	ROT
L. V.	0	120-130	100-110	75	ROT	ROA
L. S.	0	130-150	110-119	18	LOT	LOA
L. A.	0	130-150	100-115	80	LOP	LOT
D. M.*	0	120-140	100-110	120	Persistent brow	
R. A.*	0	130-160	110-119	58	LOP	LOT
M. A.	0	120-140	110-119	16	ROP	ROT
N. C.	0	120-140	110-119	15	ROP	ROA
K. P.	1	120-140	110-119	38	ROT	ROA
I. P.	0	120-150	110-119	45	LOT	OA
L. G.	0	120-140	100-119	100	OP	LOA
G. M.	2	120-140	110-119	6	LOT	LOA
A. S.	1	120-140	110-115	24	LOP	LOT
L. B.	0	130-150	105-115	32	LOT	LOA
R. P.*	2	120-140	110-119	26	ROP	ROT
K. G.*	1	130-150	100-110	36	ROP	ROA
M. K.	0	120-140	110-119	16	LOT	LOA
P. G.	1	120-140	110-115	22	LOP	LOT

*Dystocia.

†WNL, within normal limits; OP, occiput posterior; OT, occiput transverse; R, L, right or left; NSD, normal spontaneous delivery; LFD, low forceps delivery; C/S, cesarean section; Acel., accelerations.

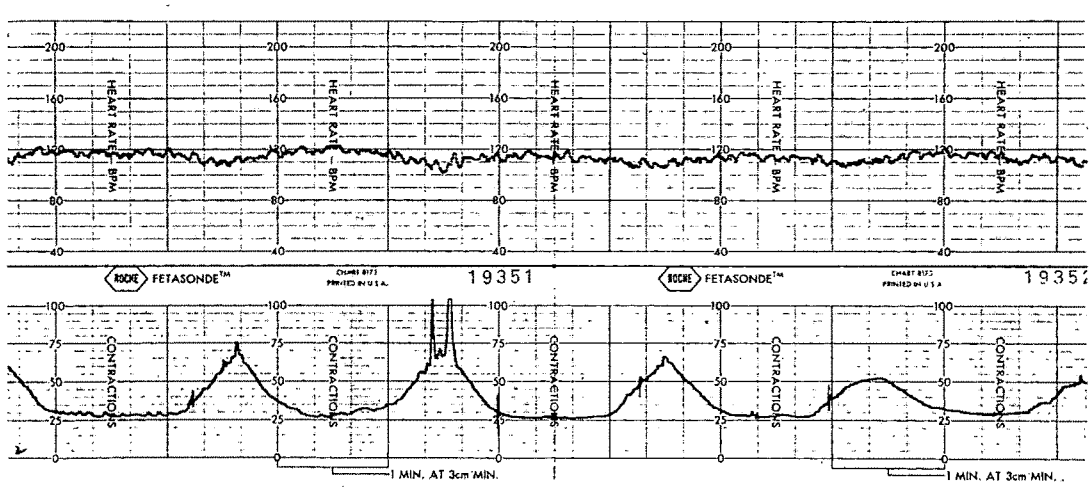


Fig. 1. Persistent moderate bradycardia also associated with early decelerations.

during the course of their labors, consistent with fetal head compression (Fig. 1).

There were five cases associated with acceleration of the FHR at the onset of each contraction, a periodic change suggesting integrity of the fetal autonomic nervous system. The remaining periodic changes were three cases of variable decelerations, one of which was associated with a nuchal cord. Ten patients showed no periodic changes.

Every patient was in active labor at the time the persistent bradycardia appeared, and many patients showed increased uterine activity during the period of bradycardia. External tocotonometry was used, precluding quantitative measurement of rises in the inten-

Associated periodic FHR changes	*Type of delivery*	*Apgar scores*	*Clinical course of neonate*
Early	LFD†	9, 10	WNL†
Early	LFD	8, 9	WNL
None	NSD	8, 9	WNL
None	NSD	9, 10	WNL
Accel.	LFD	7, 9	WNL
Accel.	LFD	9, 10	WNL
Early	LFD	8, 9	WNL
Early	NSD	9, 9	WNL
None	LFD	5, 7	WNL
Accel., early	NSD	9, 10	WNL
Accel.	NSD	9, 10	WNL
None	C/S	8, 10	WNL
None	MFD	7, 9	WNL
Accel.	LFD	8, 9	WNL
None	LFD	8, 9	WNL
Early	NSD	8, 10	WNL
Early	LFD	9, 10	WNL
None	LFD	9, 10	WNL
Early	NSD	9, 10	WNL
None	LFD	8, 9	WNL
Variable	NSD	9, 10	WNL
None	MFD	8, 9	WNL
Early	LFD	8, 9	WNL
None	NSD	9, 10	WNL
Variable	LFD	8, 9	WNL

sity of the uterine contractions. However, increased amplitude and frequency of contraction waves were noted in many cases. There were 15 occiput posterior positions, nine occiput transverse positions, and one brow presentation. Thus, every case represented an abnormal cephalic presentation in labor.

Particularly noteworthy are the normal Apgar scores and benign clinical courses of the neonates. Only one neonate had a 1 minute Apgar score below 7 in this series. This was associated with meconium-stained amniotic fluid but no FHR decelerations. This neonate also had a normal clinical course. No neonate in the series was noted to have congenital cardiac malformation or arrhythmia in the newborn period. The time from recovery of the baseline heart rate to delivery ranged from 2 hours and 10 minutes to zero in those cases with bradycardia until delivery, with no relationship to Apgar score.

Six patients showed clearly abnormal progress in labor during the period of bradycardia. These were D. M., with a persistent brow presentation requiring cesarean section; R. A., presenting as LOP, and R. P., presenting as ROP, both requiring midforceps delivery; and M. A., presenting as DOP, M. G., presenting as LOP, and K. G., presenting as ROP, all delivered by low forceps. All of these showed bradycardia for more than 30 minutes, and one for 180 minutes. Three of the six returned to a normal labor pattern after cessation of the bradycardia with subsequent low forceps delivery (Table I).

Comment

Although it is generally accepted that severe, prolonged bradycardia is frequently associated with uterine hyperactivity, uterine tetany, severe cord complications, paracervical anesthesia, and neonatal congenital cardiac lesions and arrhythmias, moderate bradycardia has not been reported with any particular clinical situation. We have found 25 cases in a 12 month period where moderate bradycardia appears to be a fetal response to relative cephalopelvic disproportion (CPD). A change in position of the fetal vertex during labor involving rotation from an unfavorable position of the vertex to a more favorable position for descent was the most common finding. Also of significance is the observation that when delivery did not immediately follow the rotation of the vertex, a return of the fetal heart rate to the normal range occurred. During these episodes, the bradycardia was not relieved by administration of oxygen or change in the position of the mother. When a change in the position of the fetal vertex occurs, the skull compression forces are alleviated, the bradycardia disappears, and normal fetal heart rate levels return. This appears to be a physiologic response to a continuous stimulus and does not seem related to fetal or neonatal hypoxia. This was demonstrated by the normal Apgar scores and benign neonatal course of these infants.

Although there is extensive literature on the effects of fetal head compression, there has been no report of the persistent moderate bradycardia described. Sureau[2] has pointed out that the pressure exerted on the fetal head between contractions is greater than the intrauterine pressure, and that this pressure is further increased when engagement is difficult due to relative cephalopelvic disproportion. Heart rate deceleration with the fetal head compression has been extensively demonstrated, and this effect persists as long as there is a significant pressure on the fetal head. Therefore, the most likely mechanism causing the bradycardia is fetal skull compression and molding due to relative cephalopelvic disproportion with malposition.

The increased uterine activity observed, the frequent association of early decelerations, and the clinical course of labor, with recovery of the baseline heart rate when the malposition was overcome, support this concept.

The pattern of moderate bradycardia is not a sign of gross fetal distress. It does correlate with abnormal position of the fetal vertex in labors affected by relative cephalopelvic disproportion. Recovery of the baseline

September 15, 1976
Am. J. Obstet. Gynecol.

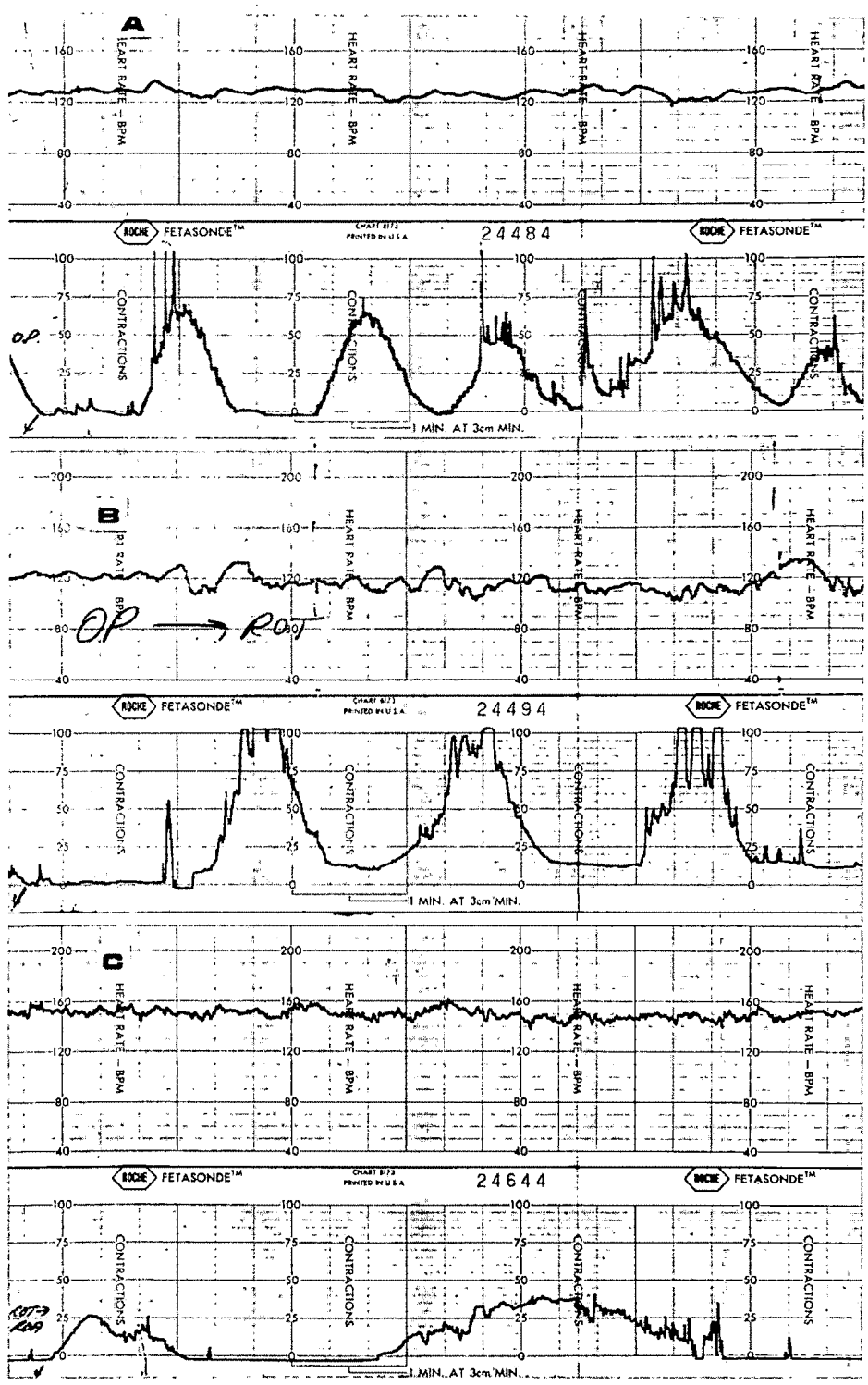


Fig. 2. The patient is gravida 2, para 1. *A*, Vertex presentation, cervix 7 cm. dilated, with ruptured membranes, station zero, direct occiput posterior position. *B*, Patient uncooperative, voluntarily pushing, cervix 7 cm. dilated, station zero, vertex rotating from direct occiput posterior position to right occiput transverse. *C*, Cervix 8 cm. dilated, station + 1, vertex rotated from right occiput transverse to right occiput anterior.

heart rate is associated with rotation of the vertex to a position overcoming the obstruction. Prolonged moderate bradycardia should indicate careful evaluation of the patient for cephalopelvic disproportion.

Addendum

Since this paper was written, six new cases of persistent moderate bradycardia have been observed with similar outcome.

REFERENCES

1. Hon, E. H.: An Introduction to Fetal Heart Rate Monitoring, 1971, p. 45.
2. Sureau, C.: The stress of labor, *In* Aladjem, S., and Brown, A. K., Editors: Clinical Perinatology, St. Louis, 1974, The C. V. Mosby Company, pp. 294-296.

Umbilical vein occlusion and transient acceleration of the fetal heart rate

Experimental observations in subhuman primates

L. STANLEY JAMES, M.D.
MING-NENG YEH, M.D.
HISAYO O. MORISHIMA, M.D., PH.D.
SALHA S. DANIEL, PH.D.
STEVE N. CARITIS, M.D.
WENDELL H. NIEMANN, D.V.M.
LEONARD INDYK, PH.D.
New York, New York

Transient acceleration of the fetal heart rate is commonly seen in the cardiotachometer tracing of the human fetus during labor. A likely cause appeared to be partial occlusion of the umbilical cord. On the basis of this hypothesis, fetal cardiovascular responses to partial occlusion of the umbilical cord or isolated intra-abdominal portion of umbilical vein were studied in near-term pregnant baboons and rhesus monkeys prior to and following sympathetic blockade with dibenzyline and propranolol. The responses were of two types. In the well-oxygenated fetus, partial occlusion resulted in transient acceleration of heart rate and a decrease in pulse pressure. This response was abolished with dibenzyline or propranolol. In the hypoxic fetus, partial occlusion resulted in either bradycardia and hypotension or hypotension with no alteration in heart rate. Thus, transient acceleration of the fetal heart rate can be explained on the basis of a sympathetic response to diminished venous return. It would appear to be an early sign of a potential cord complication. This response will not be seen if the fetus becomes asphyxiated and hypoxic.

TRANSIENT ACCELERATION of the fetal heart rate is commonly seen when the human fetus is monitored electronically during labor. This may occur during uterine contractions or may occur at irregular intervals. The cause of this transient acceleration of the fetal heart rate is not known.

On theoretical grounds, if partial occlusion of the umbilical cord resulted in compression of the umbilical vein alone, this would lead to a decrease in venous return from the placenta. The sympathetic response to this would be transient acceleration of the fetal heart rate. However, both acceleration and deceleration of the fetal heart rate have been produced experimentally in the fetal lamb or goat when the umbilical vein was partially occluded.[1–5] Bradycardia has been induced in the human fetus at cesarean section by pressure on the umbilical vein.[6]

The present research was undertaken to explore in greater detail the mechanisms involved in heart rate changes with partial or complete occlusion of the umbilical vein.

From the Division of Perinatal Medicine of the Departments of Anesthesiology, Obstetrics and Gynecology, and Pediatrics, College of Physicians & Surgeons, Columbia University and Babies Hospital, The Children's Medical and Surgical Center of New York, and the Laboratory for Experimental Medicine and Surgery in Primates.

Supported by United States Public Health Service Grant GM 09069.

Received for publication December 29, 1975.

Revised March 29, 1976.

Accepted April 9, 1976.

Reprint requests: L. Stanley James, Professor of Pediatrics, Babies Hospital, 3975 Broadway, New York, 10032.

Table I. Changes in heart rate and arterial blood pressure with partial occlusion of the intact umbilical cord or the isolated intra-abdominal UV under normal* and asphyxial* conditions

	Normal oxygenation and acid base (acceleration with partial occlusion)				*Hypoxia and acidosis (deceleration with partial occlusion)*			
	Intact umbilical cord (No. = 11)		*Intra-abdominal UV (No. = 7)*		*Intact umbilical cord (No. = 6)*		*Intra-abdominal UV (No. = 7)*	
	Control	*Occlusion*	*Control*	*Occlusion*	*Control*	*Occlusion*	*Control*	*Occlusion*
Heart rate (beats/min.)	187 ± 3.1	203 ± 3.0	180 ± 4.7	199 ± 4.0	207 ± 4.2	175 ± 9.2	213 ± 4.7	168 ± 9.3
Mean blood pressure (mm. Hg)	46 ± 0.7	43 ± 1.0	41 ± 1.1	38 ± 1.2	39 ± 2.1	35 ± 2.0	37 ± 1.7	34 ± 1.8
Δ Heart rate (beats/min.)	+16 ± 1.6†		+19 ± 1.6†		−31 ± 6.5†		−46 ± 7.7†	
Δ blood pressure (mm. Hg)	−3 ± 0.6†		−3 ± 0.4†		−4 ± 1.0†		−4 ± 0.8†	
pH_a	7.28 ± 0.010		7.32 ± 0.012		7.17 ± 0.025‡		7.15 ± 0.042‡	
Pa_{O_2} (mm. Hg)	28 ± 1.7		27 ± 1.1		20 ± 2.0‡		20 ± 2.2‡	
Sa_{O_2}	58 ± 3.4		66 ± 2.0		36 ± 5.6‡		35 ± 7.5‡	

Values = means ± standard errors.

*The particular response observed was verified by three consecutive measurements.

†Significantly different ($p < 0.001$) from control (paired t test).

‡Significantly different ($p < 0.01$) from respective normal group (Student's t test).

Material and methods

Experiments were carried out on 29 pregnant subhuman primates, baboons, and rhesus monkeys. The mean gestational age was 155 days for baboons (term, 185 days) and 149 days for rhesus monkeys (term, 168 days), respectively. Intramuscular phencyclidine hydrochloride,* 1 mg. per kilogram, was used for premedication, following which the mother was anesthetized with nitrous oxide and halothane.[7] The uterus was entered through a low transverse incision, with care being taken to avoid the area of placental implantation which could be identified visually (by increased vascularity) and by palpation (softer consistency). After partial delivery of the fetus, femoral arterial and venous catheters as well as electrocardiographic electrodes were introduced. In small fetuses, the carotid artery and jugular vein were catheterized, and a silicone rubber T-tube was inserted into the carotid artery in order that circulation to the head might remain undisturbed.

In 15 fetuses, an occluding device was placed around the umbilical cord and secured to the abdominal wall for stability. In 14 animals a paramedian incision was made in the fetal abdomen, and the intra-abdominal portion of the umbilical vein (UV) was exposed. This portion of the UV is less sensitive to manipulation and is relatively easy to approach. The occluding device was placed around the UV and secured to the abdominal wall for stability, with care being taken not to twist or distort the vessel. The fetal peritoneal cavity and abdominal wall were closed with silk sutures. The fetus was then returned to the uterine cavity, and the uterus was closed with a double-layer technique and with fine sutures to prevent subsequent leakage of amniotic fluid. In addition, amniotic fluid lost during operation was replaced in an approximate volume with normal saline. In four of these 14 animals, the occluders were applied to both the external intact cord and the UV.

Following operation, one to two hours were allowed for recovery. The mother was kept on her side and lightly sedated with a nitrous oxide–oxygen mixture and occasionally intravenous succinylcholine infusion for muscle relaxation. Diazoxide* was used to suppress uterine activity if contractions commenced.†[8] Fetal and

*Sernylan, Parke, Davis & Co., P. O. Box 118 GPO, Joseph Campau Ave. At the River, Detroit, Michigan 48232.

*Hyperstat, Schering Corp., 1011 Morris Ave., Union, New Jersey 07083.

†It was administered by slow intravenous infusion at an average rate of 0.09 mg. per kilogram per minute throughout the experiment. Fifteen animals received this treatment.

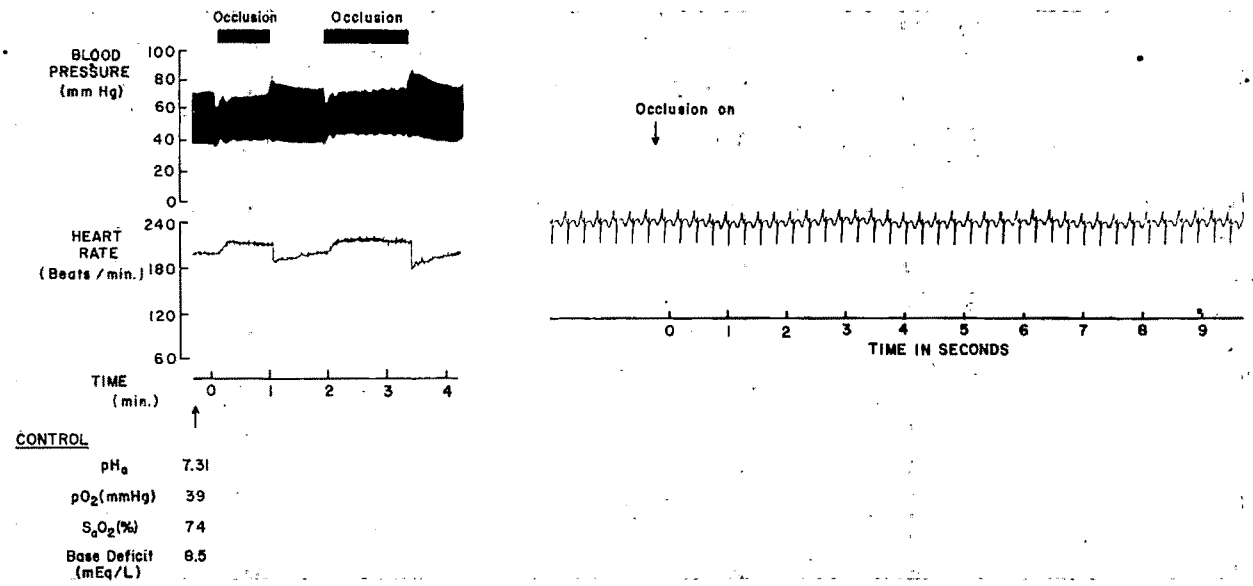


Fig. 1. Changes in arterial blood pressure, heart rate, and electrocardiogram with partial occlusion of the intact umbilical cord in a well-oxygenated baboon fetus (No. 410, 154 days' gestation). Immediate drop in blood pressure followed by elevation of heart rate was noted. There was a swift recovery of both blood pressure and heart rate after release of the cord. No significant changes in the electrocardiogram configurations with partial occlusion were seen.

maternal blood pressure, heart rate, electrocardiogram, and amniotic pressure were monitored continuously and recorded on a polygraph.* pH and blood gases were determined serially with electrodes† and base deficit was calculated from the Siggaard-Andersen[9] nomogram. Oxygen saturation was calculated from PaO_2 and pH_a.[10, 11]

With the fetus in utero, the umbilical cord or isolated UV was partially occluded by injecting water (0.3 to 0.6 ml.) into the cuff of the occluding device for periods ranging from 0.2 to 7.7 minutes. The amount of fluid necessary to cause complete or partial occlusion of umbilical cord or UV was determined in the initial experiments by inflating the cuff prior to and after placement and under direct vision. The smallest amount of water necessary to induce a response was used, and the same degree of occlusion was induced for every test period. Occlusion was induced only when uterine contractions were absent or minimal. If uterine contractions were present, occlusion was induced only during the interval between contractions.

The role of the sympathetic nervous system in the response to partial umbilical vein occlusion was studied in 10 fetuses. Five of these received a bolus dose of dibenzyline, 5 mg. per kilogram intravenously, and five received propranolol, 1 mg. per kilogram intravenously.[12] The UV was partially occluded prior to and following the administration of the sympathetic blocking agent. To study the response to complete UV occlusion (eight fetuses), 1.5 to 2.0 ml. of water was injected into the cuff. For purposes of statistical evaluation, the paired t test was used to compare changes from control within any one group of fetuses, each fetus serving as its own control. In addition, Student's t test was used to compare results between two groups.

Results

The responses to partial occlusion of the umbilical cord or UV and the effect of sympathetic blockade were similar in the fetuses of both the baboon and rhesus monkey. Therefore, the results have been combined for analysis. The responses were of two types, depending on the acid-base state and oxygenation of the fetus (Table I and Figs. 1, 2, and 3).

In the nonasphyxiated group (normal oxygenation and acid base), a small fall in blood pressure (mean, 3 mm. Hg) was consistently seen with partial occlusion and was accompanied by a significant increase in heart rate of 16 to 19 beats per minute ($p < 0.001$). There was a small fall in PaO_2 ($p < 0.05$) but no significant

*Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, California 92634.

†Radiometer, London Co., 811 Sharon Dr., Cleveland, Ohio 44145.

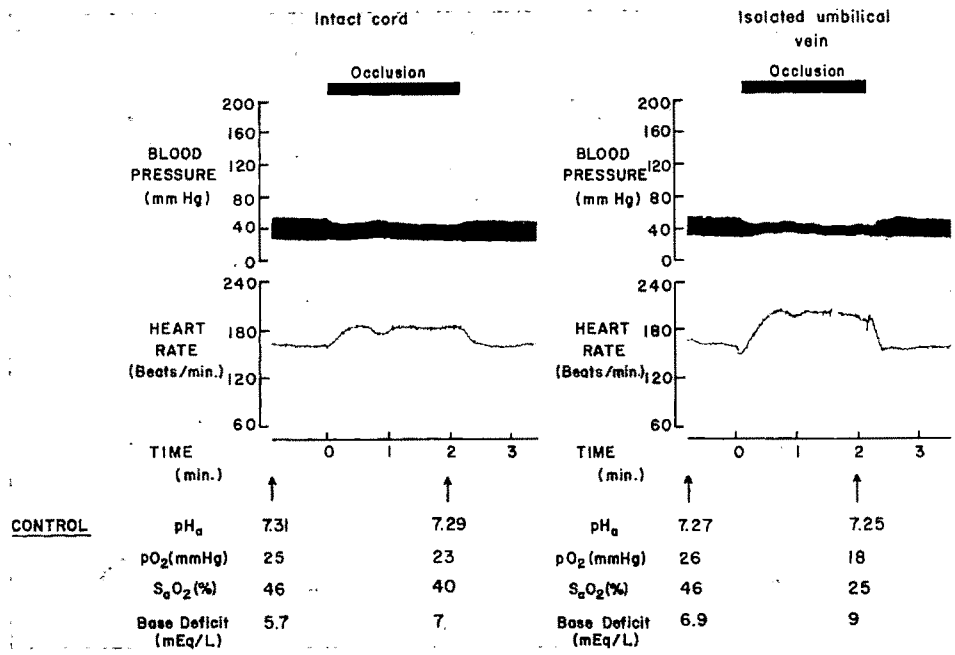


Fig. 2. Changes in blood pressure and heart rate with partial occlusion of the intact umbilical cord and the isolated intra-abdominal portion of the UV in the same baboon fetus. A similar response occurred with both methods of partial occlusion.

change in pH_a or $PaCo_2$ during the period of partial occlusion in the nonasphyxiated group (Table II). When the occluder was released, there was a prompt rise in blood pressure and fall in heart rate to control levels.

In the asphyxiated group (hypoxic and acidotic), a small fall in blood pressure (mean, 4 mm. Hg) was also consistently seen with partial occlusion, but this was accompanied by a decrease or no alteration in heart rate. The mean fall in heart rate of 38 beats per minute was significant ($p < 0.001$). The particular response observed was verified by three consecutive measurements. When the occluder was released, there was a prompt recovery of blood pressure to the control level, but the recovery of the heart rate was delayed, the delay being more prolonged with severe asphyxia. These two types of heart rate response are shown in the same animal in Fig. 3; the heart rate rose with partial occlusion when the fetus was well oxygenated and fell when it was hypoxic.

Following a bolus injection of dibenzyline (5 mg. per kilogram intravenously) or propranolol (1 mg. per kilogram, intravenously), transient acceleration of the fetal heart rate with partial occlusion of the UV did not occur in any instance (Figs. 4 and 5). There was either prompt bradycardia together with hypotension or no change in heart rate.

Table II. Changes in acid-base state and blood gases during partial occlusion of the intact umbilical cord or isolated umbilical vein in fetuses showing an acceleration of heart rate

	Before occlusion	*With partial occlusion*
pH_a	7.30 ± 0.011	7.29 ± 0.014
Pa_{O_2} (mm. Hg)	27 ± 1.5	23 ± 1.0*
$Paco_2$ (mm. Hg)	39 ± 2.1	41 ± 2.6
Base Deficit (mEq./L.)	6.9 ± 0.74	6.6 ± 0.90

No. = 11. Mean duration of occlusion: 3.4 minutes.
*$p < 0.05$.

With complete occlusion of the UV (Fig. 6), there was initial tachycardia with hypotension. This was soon followed by marked bradycardia.

Because diazoxide has some properties similar to those of drugs which have beta-sympathomimetic activity, there is a possibility that the heart rate responses might have been modified by diazoxide in those experiments when it was administered. The base-line heart rate and increase in fetal heart rate with partial occlusion of the umbilical cord or UV were similar in the 15 animals which received diazoxide (from 181 to 199 beats per minute) to that observed in animals not

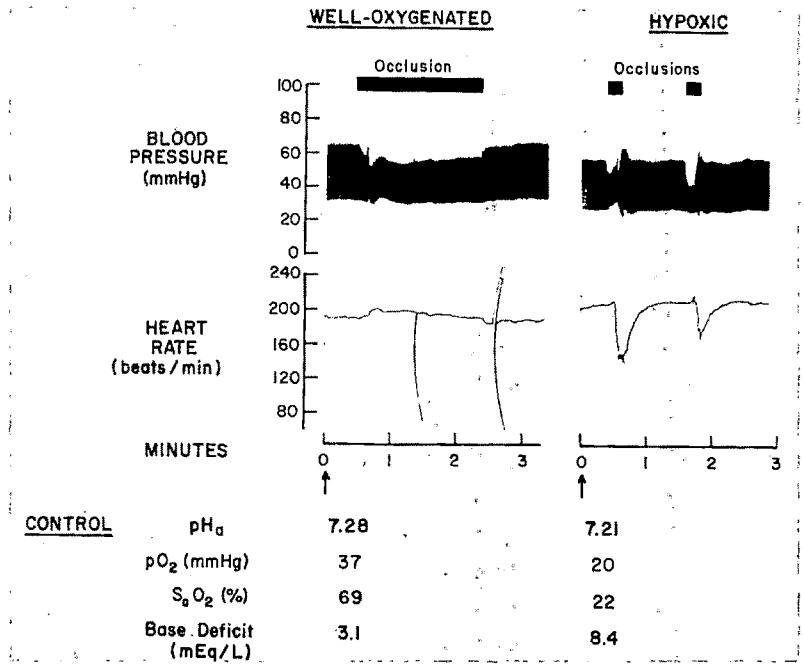


Fig. 3. Changes in blood pressure and heart rate with partial occlusion of the intact umbilical cord of a fetal baboon under well-oxygenated and hypoxic conditions (No. 72, 148 days' gestation). A transient acceleration of the heart rate was seen in the well-oxygenated state, and deceleration of the heart rate occurred during hypoxia.

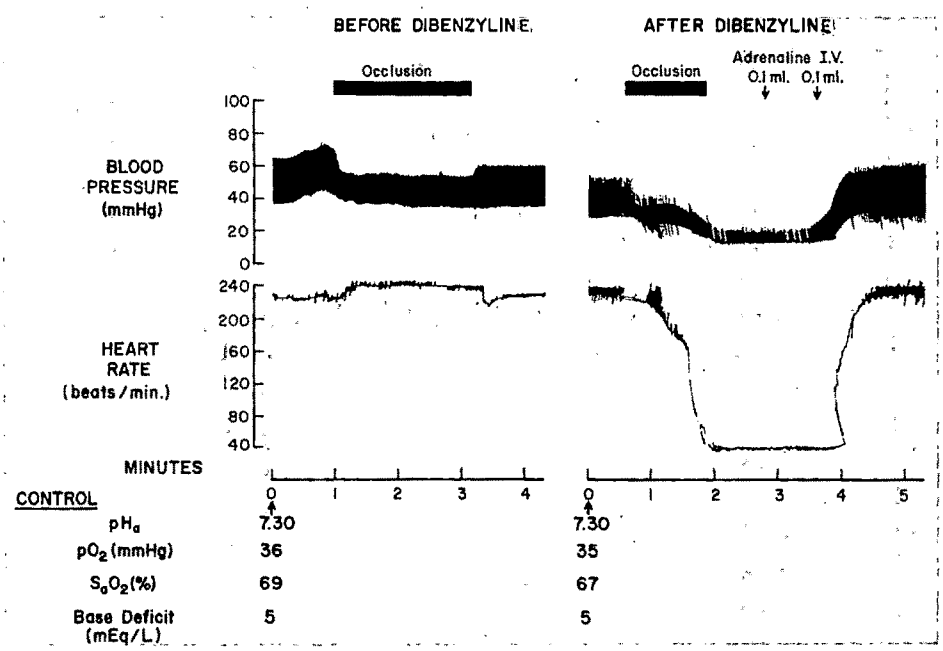


Fig. 4. Changes in blood pressure and heart rate with partial occlusion of the isolated UV in a well-oxygenated fetal baboon before and after intravenous administration of dibenzyline (5 mg. per kilogram) (No. 102, 157 days' gestation). No increase in heart rate occurred after administration of dibenzyline. The fall in blood pressure was more marked after blockade of the α-receptors. Recovery occurred after administration of epinephrine (0.1 mg. intravenously).

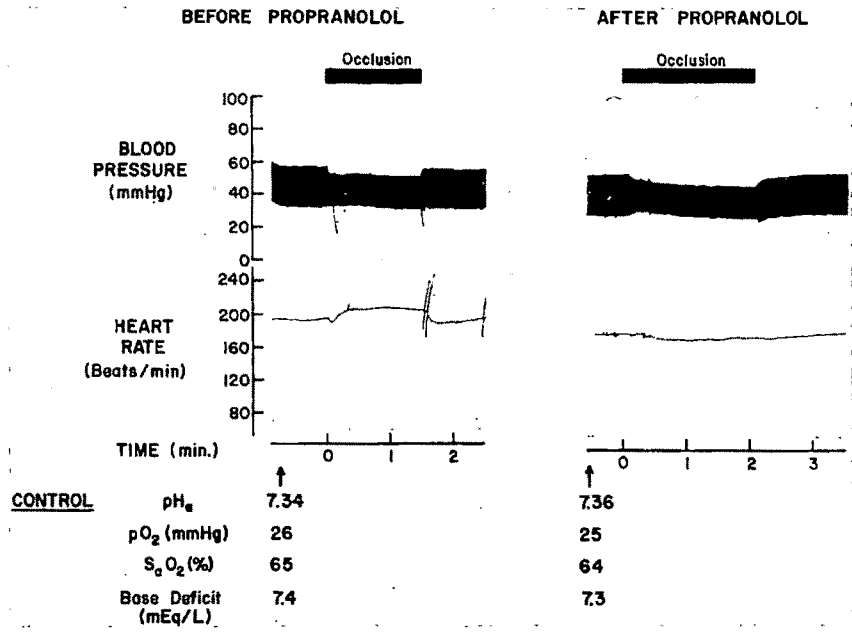


Fig. 5. Changes in blood pressure and heart rate with partial occlusion of the isolated UV in a well-oxygenated baboon fetus before and after intravenous administration of propranolol (1 mg. per kilogram) (No. 102, 160 days' gestation). Propranolol eliminated the transient acceleration of the heart rate with partial occlusion though the fetus was still well oxygenated.

receiving the drug (from 190 to 210 beats per minute). This lack of effect of diazoxide on the fetal heart rate was probably related to the very small dose given.

Comment

These experiments have demonstrated that partial occlusion of the umbilical cord or the umbilical vein in subhuman primates can cause an increase in heart rate and a fall in blood pressure when the fetus is in good condition. A similar response was seen whether the isolated UV or intact umbilical cord was partially occluded. This response was not seen when the fetus was hypoxic and acidotic or when the sympathetic nervous system was blocked pharmacologically with dibenzylene and propranolol. Thus, one cause of transient acceleration of fetal heart rate appears to be a sympathetic response to diminished venous return from the placenta. In contrast, complete occlusion of the umbilical cord causes hypertension and severe bradycardia with various degrees of myocardial conduction defects.[13]

Therefore, the sympathetic response of the fetal heart appears to be quite active in the fetus of the subhuman primate during the later stages of development (84 per cent of gestation in baboons and 89 per cent in rhesus monkeys). In other species, it has been

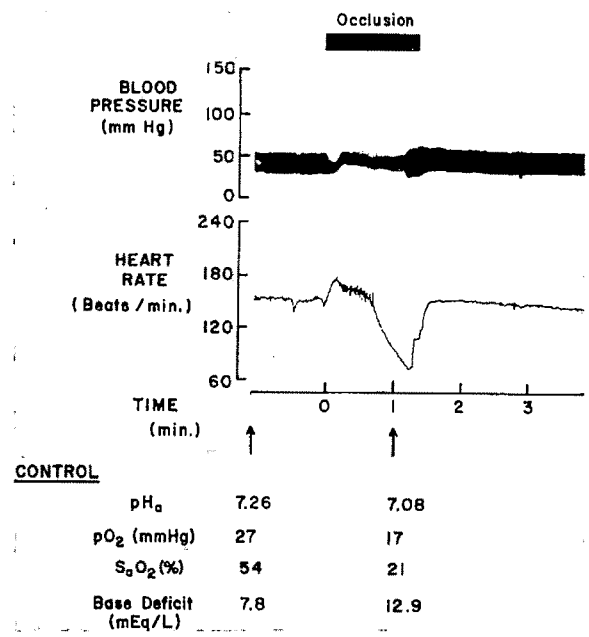


Fig. 6. Changes in blood pressure and heart rate with complete occlusion of the isolated UV in a well-oxygenated baboon fetus (No. 124, 154 days' gestation). An initial acceleration of the heart rate was seen. This was followed by profound bradycardia as the fetus became hypoxic. Slight elevation of diastolic pressure was seen, probably due to an α-sympathetic effect.

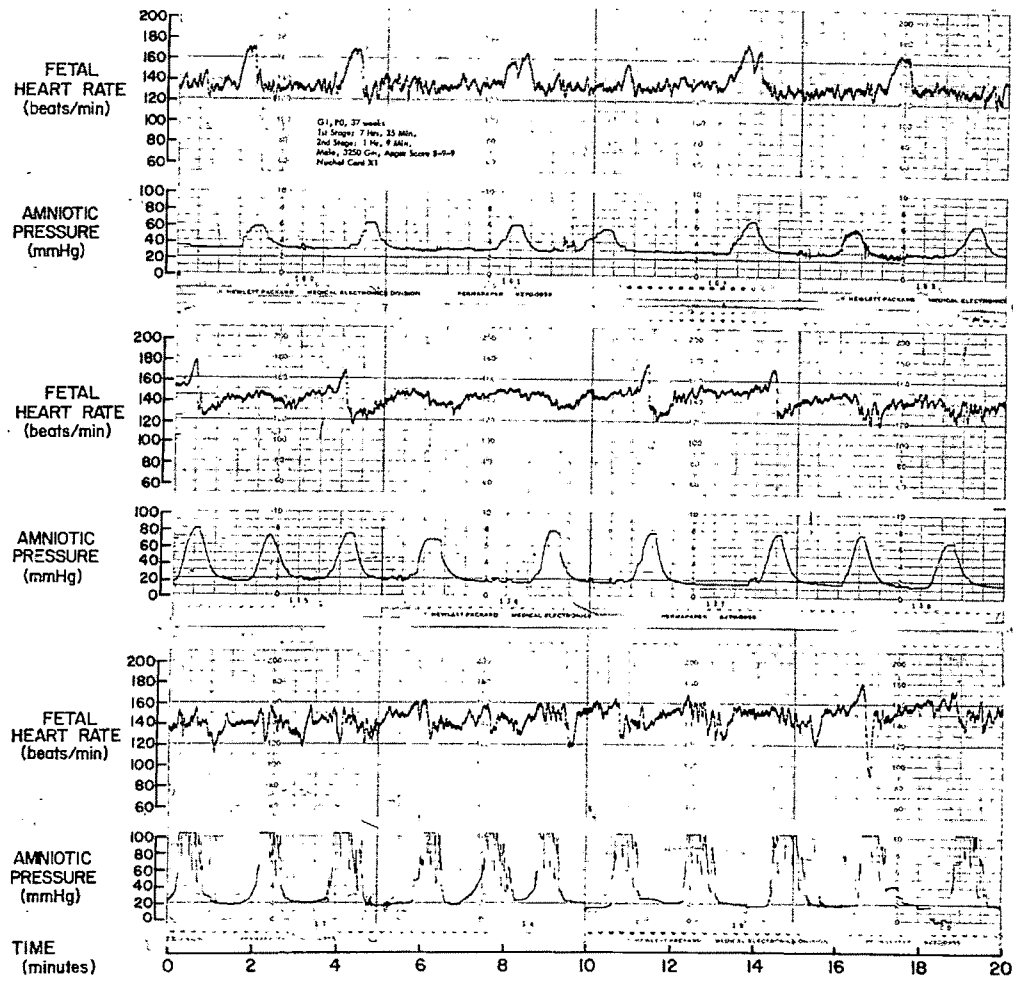


Fig. 7. An example of transient acceleration of the heart rate in a human fetus during labor. It progressed to a variable deceleration pattern as labor advanced. At delivery, the umbilical cord was around the neck.

shown that beta-sympathetic activity of the cardiovascular system increases rapidly after 80 per cent of gestation.[12] In man, the cardiovascular response to various stimuli during labor appears to be diminished prior to 32 weeks (80 per cent of gestation) but active after that time.[14]

A mild degree of hypoxia which can also cause acceleration of fetal heart rate might have contributed to the response observed in our experiments.[1, 2] However, it was not a major factor, since acceleration of fetal heart rate was seen without any concomitant change in oxygen saturation in some experiments. When the fetus was more hypoxic and acidotic, partial occlusion of the umbilical vein caused bradycardia and hypotension.

Therefore, our experiments provide an explanation for previous observations in which both tachycardia[1, 2, 5] and bradycardia[3–5] have been observed to occur with partial occlusion of the umbilical vein in the fetal lamb or goat and for the bradycardia observed with partial occlusion of the umbilical vein at cesarean section in the human subject by Lee and Hon.[6] These responses are probably due to the interaction of several separate mechanisms. The baroreceptor response to hypotension is tachycardia. The chemoreceptor response to mild hypoxia is tachycardia[1] and that to severe hypoxia is bradycardia.[1, 15, 16] Finally, the release of catecholamines with hypoxia may also play a role.[17] Thus, depending on circumstances, an interplay of these mechanisms will result in either tachycardia or bradycardia as demonstrated in our experiments.

With a complete or severe degree of occlusion of UV, the cardiovascular response is initially acceleration of the fetal heart rate, the sympathetic response to diminished venous return. This is soon followed by a deceleration reflecting the development of severe hypoxia as the result of cessation of oxygenated blood returning from the placenta to the fetus.

In reviewing records of the fetal heart rate during labor, in the near-term fetus, acceleration appears to be one of the most common patterns seen (Fig. 7) and has been related clinically to an abnormal position of the umbilical cord.[18] Acceleration of the fetal heart rate is also seen in conjunction with fetal scalp sampling, but the duration of response is considerably longer than the response seen in Fig. 7. The major cause of recurring transient episodes of tachycardia with or without uterine contraction is likely to be partial occlusion of the umbilical vein and reduced venous return from the placenta. It can be taken as an early warning sign of impending cord complication and will be observed only when the fetus is in good condition with a responsive autonomic nervous system. This response, namely, acceleration of the heart rate, is reduced or abolished as the fetus becomes more severely hypoxic and acidotic.

REFERENCES

1. Born, G. V. R., Dawes, G. S., and Mott, J. C.: Oxygen lack and autonomic nervous control of the foetal circulation in the lamb, J. Physiol. **134:** 149, 1956.
2. Dawes, G. S., and Mott, J. C.: Changes in O_2 distribution and consumption in foetal lambs with variations in umbilical blood flow, J. Physiol. **170:** 524, 1964.
3. Reynolds, S. R. M.: Bradycardia in the lamb fetus in response to circulatory distress, Am. J. Physiol. **176:** 169, 1954.
4. Goodwin, J. W., Mahon, W. A., Reid, and D. W. J.: Effect of graded reduction of umbilical blood flow on right and left ventricular outputs in the fetal lamb, Circ. Res. **22:** 595, 1968.
5. Towell, M. E., and Salvador, H. S.: Compression of the umbilical cord: An experimental model in the fetal goat, *in* Fetal Evaluation During Pregnancy and Labor, London, 1971, Academic Press, Inc., p. 143.
6. Lee, S. T., and Hon, E. H.: Fetal hemodynamic response to umbilical cord compression, Obstet. Gynecol. **22:** 553, 1963.
7. Morishima, H. O., Hyman, A. I., Adamsons, K., and James, L. S.: Anesthetic management for fetal operation in the subhuman primate, Am. J. Obstet. Gynecol. **110:** 926, 1971.
8. Morishima, H. O., Cohen, H., Brown, W. U., Daniel, S., Niemann, W. H., and James, L. S.: The inhibitory action of diazoxide on uterine activity in the subhuman primate: Placental transfer and effect on the fetus, J. Perinat. Med. **1:** 13, 1973.
9. Siggaard-Andersen, O.: Blood acid-base alignment nomogram, Scand. J. Clin. Lab. Invest. **15:** 211, 1963.
10. Novy, M. J., Parer, J. T., and Behrman, R. E.: Equations and nomograms for blood-oxygen dissociation curves in adult and fetal macaques, J. Appl. Physiol. **26:** 339, 1969.
11. Paton, J. B., Peterson, E., Fisher, D. E., and Behrman, R. E.: Oxygen dissociation curves of fetal and adult baboons, Res. Physiol. **12:** 283, 1971.
12. Vapaavouri, E. K., Shinebourne, E. A., Williams, R. L., Heymann, M. A., and Rudolph, A. M.: Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs, Biol. Neonate **22:** 177, 1973.
13. Yeh, M. N., Morishima, H. O., Niemann, W. H., and James, L. S.: Myocardial conduction defects in association with compression of the umbilical cord. Experimental observation on fetal baboons, Am. J. Obstet. Gynecol. **121:** 951, 1975.
14. Stark, R. I., Rey, H., Dwarka, R., and James, L. S.: A new approach to predicting the hi-risk neonate. A scoring system for intrapartum monitoring, (Presented to the Society for Pediatric Research, April, 1976. (Abst.)
15. Dawes, G. S., Duncan, S. L. B., Lewis, B. V., Merlet, C. L., Owen-Thomas, J. B., and Reeves, J. T.: Hypoxaemia and aortic chemoreceptor function in foetal lambs, J. Physiol. **201:** 105, 1969.
16. Cohn, H. E., Sacks, E. J., Heymann, M. A., and Rudolph, A. M.: Cardiovascular responses to hypoxemia and acidemia in fetal lambs, Am. J. Obstet. Gynecol. **120:** 817, 1974.
17. Comline, R. S., and Silver, M.: The release of adrenaline and noradrenaline from the adrenal glands of the foetal sheep, J. Physiol. **156:** 424, 1961.
18. Goldkrand, J. W., and Speichinger, J. P.: "Mixed cord compression," fetal heart rate pattern, and its relation to abnormal cord position, Am. J. Obstet. Gynecol. **122:** 144, 1975.

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Successful case of transfusion. Observations on transfusion of blood with a description of his gravitator

JAMES BLUNDELL

The Lancet, vol. 1, pp. 431-432, and vol. 2, pp. 321-324, 1828-1829



THE LANCET.

Vol. II.] LONDON, SATURDAY, JUNE 13, [1828-9.

OBSERVATIONS
ON
TRANSFUSION OF BLOOD.

By Dr. Blundell.

*With a Description of his Gravitator.**

States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed; and still more frequently with cases which seem to require a supply of blood, in order to prevent the ill health which usually arises from large losses of the vital fluid, even when they do not prove fatal.

In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore it seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

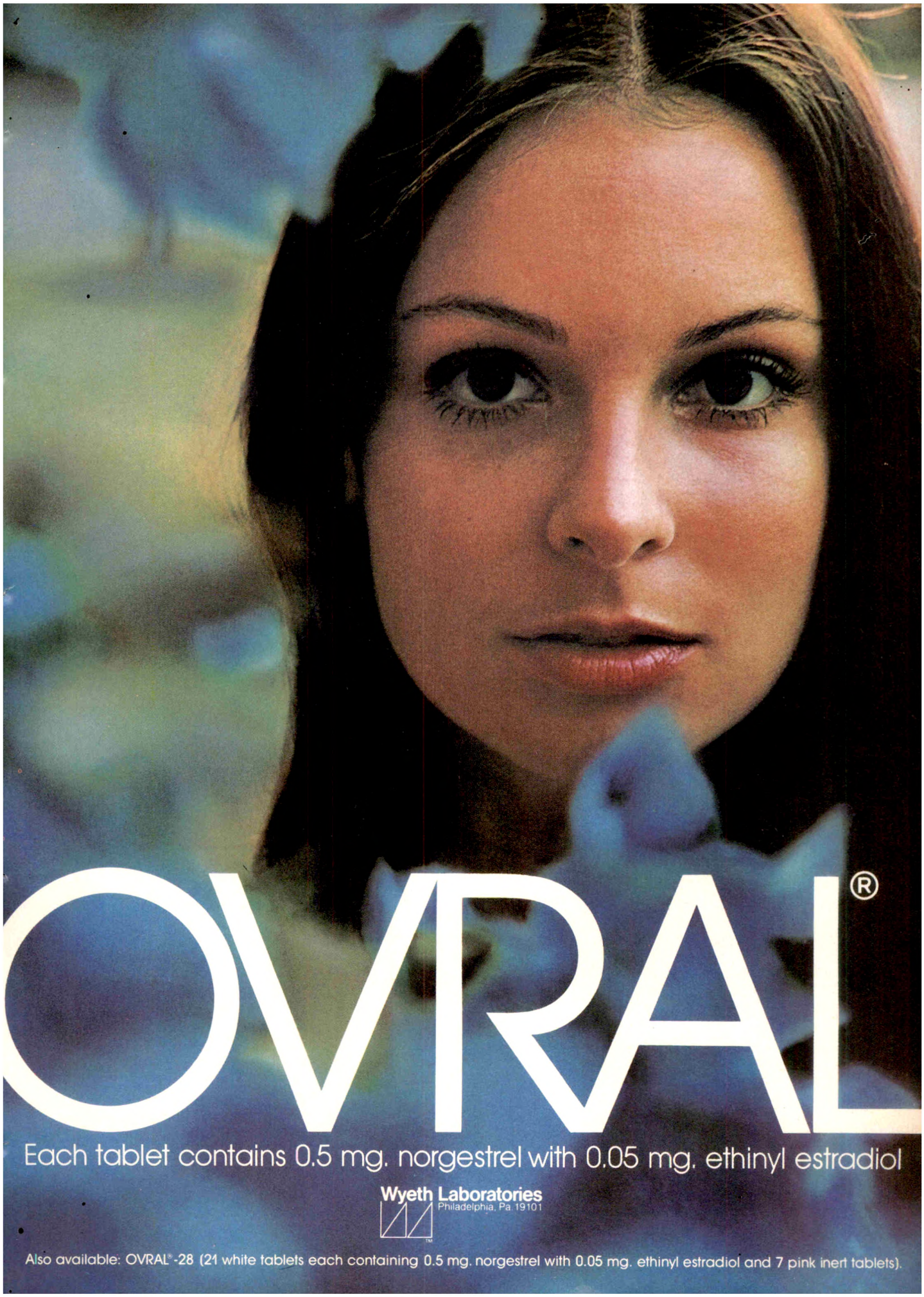
The following plate represents the whole apparatus connected for use and in action:—

* The instrument is manufactured by Messrs. Maw, 55, Aldermanbury.

Tab. 1.

No. 302. Y

The first successful transfusion in modern times was in a patient with severe postpartum hemorrhage. She had bled heavily about an hour and a half following the delivery of her third child. Pressure was applied to the abdomen; ice was placed into the vagina, and brandy and port wine were administered, but the patient appeared to be dying. Blundell, physician and obstetrician at Guy's and St. Thomas Hospitals, London, was appalled at his helplessness in combating fatal hemorrhage associated with delivery and had developed techniques for just such a case. By a series of careful experiments in animals, he established that bloods of different species were incompatible, so that a person should be given blood only from another human subject. He also showed that after extreme exsanguination replacement of only a fraction of the amount lost was needed to effect recovery. In addition, he invented various syringes, funnels and other devices for performing indirect transfusion. A fellow surgeon, Mr. Davies, underwent venesection, and the stream of blood was directed into the "gravitator," a device of Blundell's invention (see illustration). The patient received about 8 ounces of blood through a thin silver tube in a vein of the forearm over a three-hour period. Blundell wrote, "It was not until the whole quantity had been thrown in, that there was any decided amendment in the condition of the patient, she then rallied, and became in every respect better. Her convalescence has been gradual, and at this time, eleven days after delivery, she is doing well. There has been some tumefaction, and likewise pain of the arm, in which the transfusion was made; but these have subsided. It is worthy of notice that the patient expresses herself very strongly on the benefits resulting from the injection of the blood; her observations are equivalent to this—that she felt as if life were infused into her body." It is claimed that Blundell performed 10 transfusions in all (including two in patients who were already dead), probably only four of which were successful. Of course, the idea of transfusion was not new. Richard Lower, in 1665 (Philosoph. Trans. 1: 353, 1665-1666), successfully transferred blood from one dog to another. Because of the formidable problems of coagulation, storage, and typing, it was not until World War II that blood replacement became a practical procedure.


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol
Wyeth Laboratories
Philadelphia, Pa. 19101
Also available: OVRAL®-28 (21 white tablets each containing 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol and 7 pink inert tablets).



Estrogen as natural to her body as the estrone it restores

OGEN®
(PIPERAZINE ESTRONE SULFATE)

Helps you arrive at the minimum estrogen dosage needed to relieve her symptoms



One Divide-Tab® tablet may well be the correct dosage but only trial can tell.



Some patients may require only half this dosage for relief of symptoms.



Other patients may experience partial relief of symptoms when a half-tablet more would provide complete control.

In short: Divide-Tab tablets help you determine how much is needed and how little is enough . . . with one prescription.

6053143

See following page for Brief Summary.

ABBOTT

OGEN® PIPERAZINE ESTRONE SULFATE

offers you four Divide-Tab® dosage strengths for greater flexibility



OGEN .625
(piperazine estrone sulfate 0.75 mg., calculated as sodium estrone sulfate 0.625 mg.)



OGEN 1.25
(piperazine estrone sulfate 1.5 mg., calculated as sodium estrone sulfate 1.25 mg.)



OGEN 2.5
(piperazine estrone sulfate 3 mg., calculated as sodium estrone sulfate 2.5 mg.)



OGEN 5
(piperazine estrone sulfate 6 mg., calculated as sodium estrone sulfate 5 mg.)

6053143R1

Brief Summary

Important Notes: It has now been conclusively established that the use of oral contraceptives containing estrogens and progestins is associated with an increased risk of thromboembolic disease. Retrospective studies have shown a statistically significant association between the use of these drugs and thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism. This conclusion is based on three principal studies[1-3] done in Great Britain and one[4] done in the U.S. Based on these studies it has been estimated that users of oral contraceptives are four to seven times more likely than nonusers to develop thromboembolic disease with no evident cause. The American study also indicated that the increased risk did not persist after the drug was discontinued, nor was it enhanced by long-term administration. Although this study was not designed to evaluate a difference between products, the results suggested that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis[5] of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen in the oral contraceptive used. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles to use the smallest effective dose of estrogen in treating patients, whenever feasible.

The degree of risk associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate has not yet been satisfactorily determined.

Long-term administration of both natural and synthetic estrogens in multiples of the human dose to subprimate animal species increases the frequency of some animal carcinomas. Conclusions based on these data cannot be applied directly to man. The possible carcinogenicity of the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued.

It has been reported in a recent study[6] done in the United States that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of the development of vaginal adenocarcinoma years later in the exposed offspring.

Indications: OGEN (piperazine estrone sulfate tablets) is indicated:—For replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure. In the management of senile vaginitis; in kraurosis vulvae with or without pruritus.

For the prevention of postpartum breast engorgement.

In the management of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

In inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: Estrogens are contraindicated in patients with known or suspected carcinoma of the breast, except in those cases of progressive disease not amenable to surgery or irradiation occurring in women who are at least five years postmenopausal or in men in whom castration is not feasible. They are also contraindicated in patients with other known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium.

These drugs are further contraindicated in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions, in patients with markedly impaired liver function, and in those with undiagnosed, abnormal genital bleeding.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected, the drug should be discontinued immediately. If there is a sudden onset of proptosis, diplopia, or migraine, the medication should be discontinued pending an examination. If papilledema or retinal vascular lesions are found, the medication should be withdrawn.

Estrogens may be excreted in the mother's milk, and an estrogenic effect upon the nursing infant has been described. The long range effect on the infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This effect is not dependent on dose or immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Precautions: Because normal endogenous hormone production varies among individuals, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, or other effects (see ADVERSE REACTIONS).

Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

If any unexplained or excessive vaginal bleeding occurs during estrogen therapy, nonfunctional causes should be considered. The drug should be discontinued and a thorough investigation made of the cause, being certain to ascertain that a malignancy is not present.

Pre-existing uterine fibromyomata may increase in size with estrogen therapy; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

A pre-treatment physical examination should include special attention to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. Estrogens should be used cautiously in women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast.

To avoid this, oral estrogens should be administered cyclically to the menopausal or hypogonadal patient.

Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Estrogens influence the metabolism of calcium and phosphorus and should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is not complete. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Urinary stress incontinence may occur when large doses of estrogens are used in nonpregnant women.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient receiving an estrogen, it is recommended that they be repeated after the drug has been withheld for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function will require further study.

Adverse Reactions: Although not all of the following reactions have been specifically associated with OGEN (piperazine estrone sulfate tablets), they have been reported with estrogens generally and may be encountered when giving any estrogen.

Gastrointestinal: nausea, anorexia, vomiting, abdominal cramps, bloating, cholestatic jaundice and increase or decrease in body weight.

Genitourinary: sodium and water retention, breakthrough bleeding, spotting, and withdrawal bleeding, increased cervical mucus, reactivation of endometriosis, and cystitis-like syndrome.

Endocrine: breast swelling and tenderness, possible diminution of lactation when given immediately postpartum, increased blood sugar levels, and decreased glucose tolerance.

Central Nervous System: headaches, mental depression, increase or decrease of libido, nervousness, dizziness, fatigue irritability and malaise.

Dermatologic-Hypersensitivity: loss of scalp hair, allergic reactions and rashes, hemorrhagic eruption, itching, erythema nodosum, and erythema multiforme.

Musculoskeletal: backache.

Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches.

Hematologic: a statistically significant association has been demonstrated between the use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neurooocular lesions (e.g., retinal thrombosis and optic neuritis).

Miscellaneous: premenstrual-like syndrome and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

ABBOTT

Why make side effects part of your prescription...



recommend safe and proven conception control

Koromex products have been delivering effective spermicidal qualities for almost 50 years. They rarely have any contraindications. And, Koromex products are simple and comfortable to use. Both coil and arcing spring diaphragms are available.

Write for starter packages.

Holland-Rantos Co., Inc.

A Division of Youngs Drug Products Corp.

P.O. Box 5, Piscataway, N.J. 08854

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

> *"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."*

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY
TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.
A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

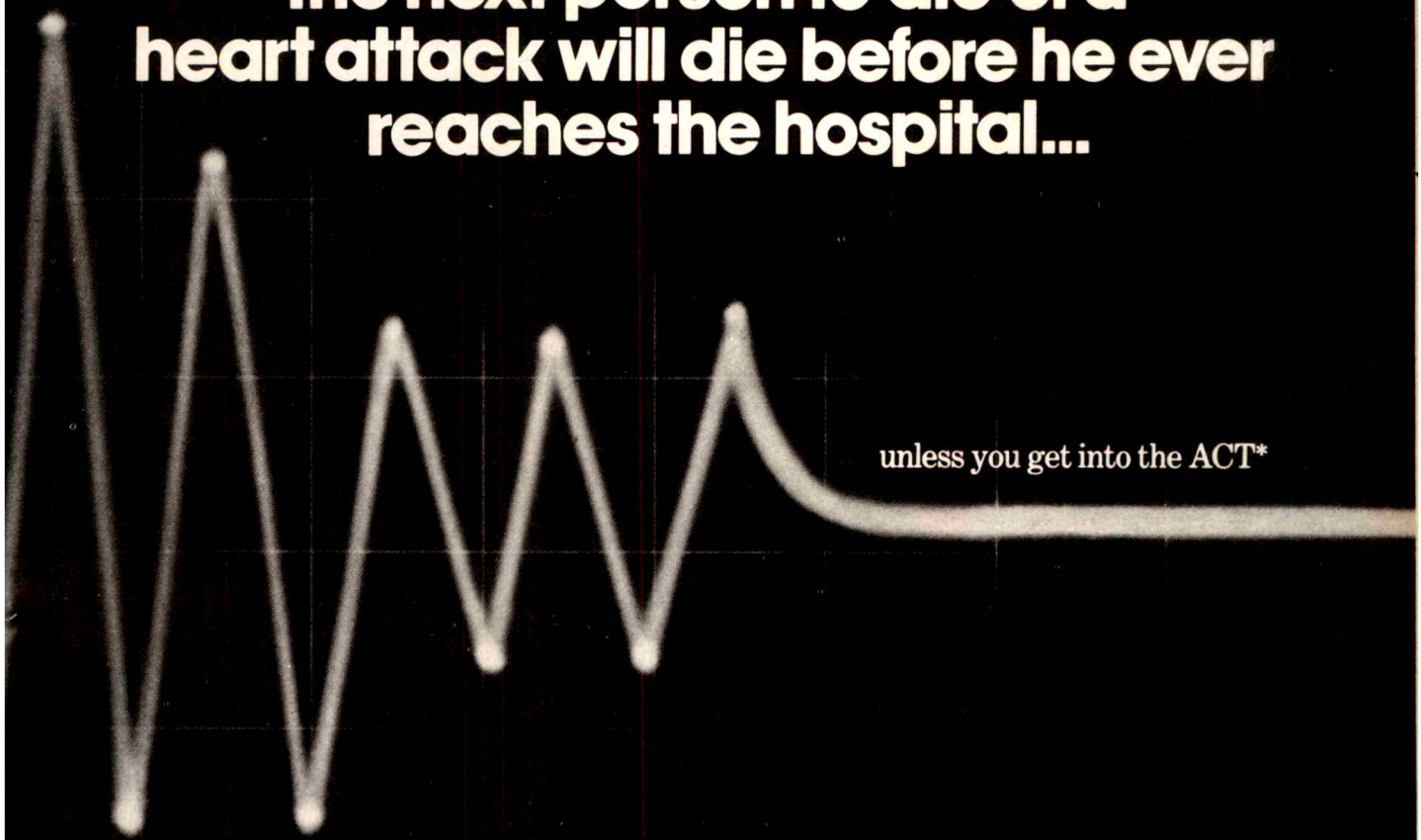
☐ **NEW SIZE (8¼″ × 11″) for 1975 copies**
☐ **OLD SIZE (7¼″ × 10½″) for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____

Chances are 50/50 the next person to die of a heart attack will die before he ever reaches the hospital...



unless you get into the ACT*

You could be instrumental in bringing Mobile Coronary Care to your community.
We can help you.
We have the facts, figures, and a blueprint for action.
Write us...

***ACT FOUNDATION**
(Advanced Coronary Treatment)
350 Grove Street
Somerville, New Jersey 08876

The ACT Foundation —sponsored as a public service by twelve leading pharmaceutical companies.

ACT Foundation
350 Grove Street
Somerville, New Jersey 08876

Please send me information on how I can help establish a Mobile Coronary Care System in my community.

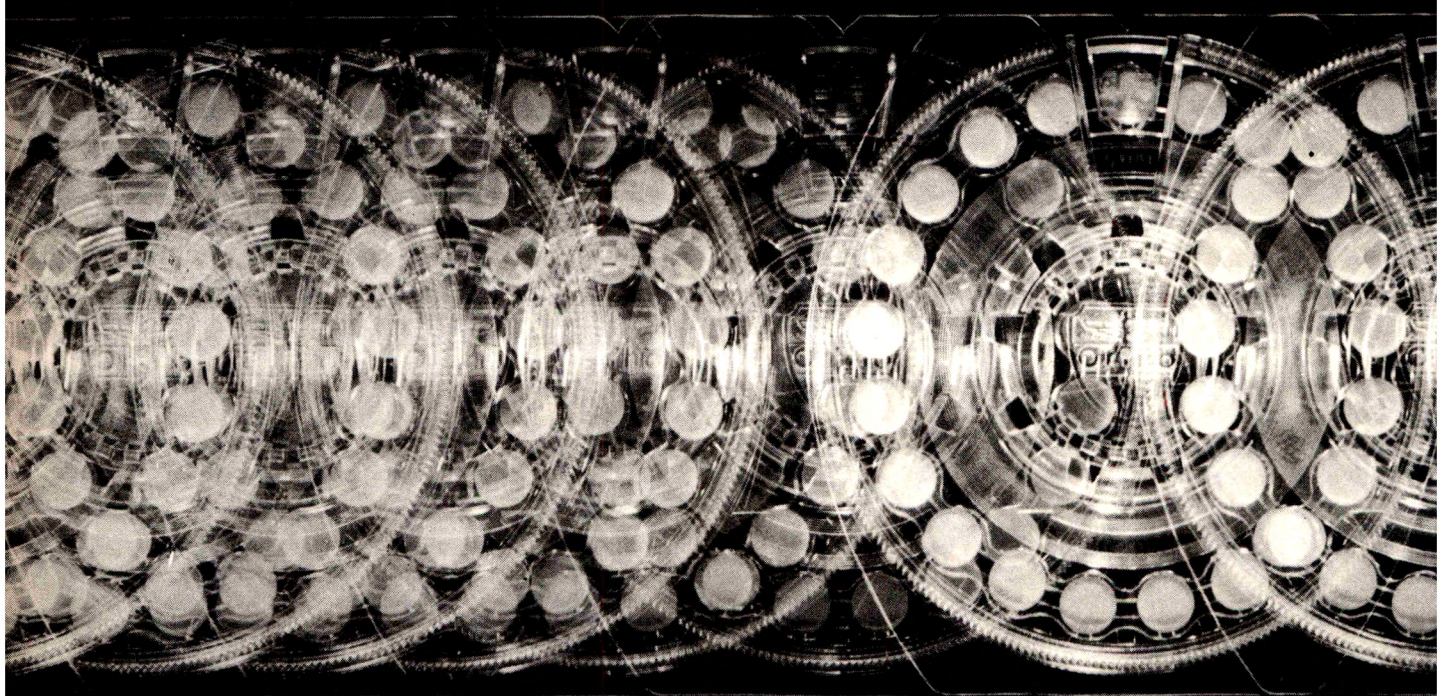
Name _____

Address _____

City _____ State _____ Zip _____

D-14084-4

IMPORTANT
ANNOUNCEMENT



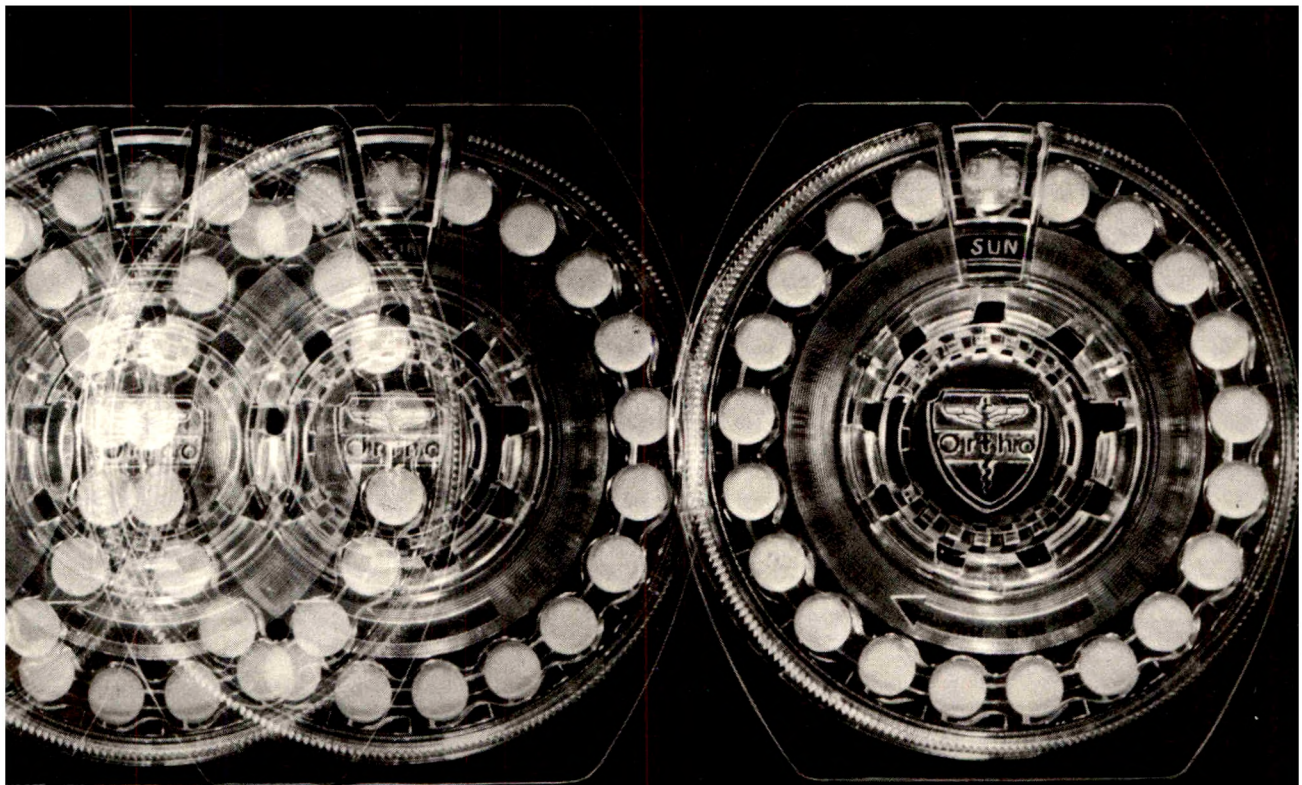
ModiCon

TRADEMARK

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.
In the 28-day regimen, each green tablet contains inert ingredients.

to offer lower-dose oral contraception with higher-dose effectiveness

© Ortho Pharmaceutical Corporation, 1976



is back.

Reformulated without dye *ModiCon is back, but without the coloring agent. Quality control testing on new white ModiCon demonstrates excellent stability.*

No change in hormonal content *Alterations in the hormonal content were not necessary. ModiCon still contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.*

Same clinical benefits *ModiCon is back in a new white tablet to offer the same clinically documented benefits as before: low hormonal intake – highly effective – well tolerated† – and the only lower-dose combination available in the unique DIALPAK* Tablet Dispenser.*

Two regimens *Available in both 21 and 28-day regimens.*

†It should be noted that pregnancy rates are usually derived from studies conducted by different investigators in several population groups and they cannot be compared with precision.

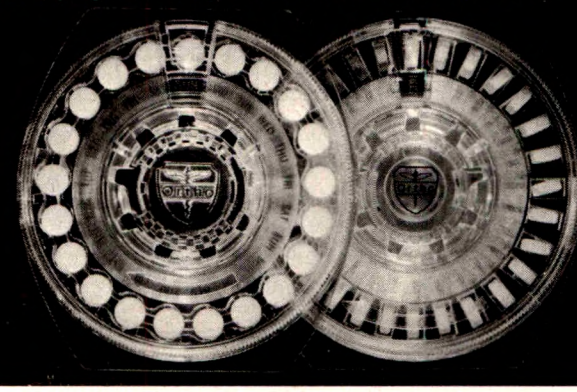
‡Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

Please turn page for full prescribing information.

*TRADEMARK

ModiCon TRADEMARK is back.

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.



In both 21 and 28-day regimens

Description: Each MODICON Tablet contains 0.5 mg of the progestational substance, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

Each green tablet in the 28-day regimen contains inert ingredients.

Actions: MODICON acts through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of MODICON.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with MODICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of MODICON in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with MODICON. Therefore, if such tests are abnormal in a patient taking MODICON, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged MODICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving MODICON therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with MODICON may mask the onset of the climacteric. 10. The pathologist should be advised of MODICON therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steriods. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, MODICON should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during MODICON therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: **1.** Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health: 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.L.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:241-245, May 3, 1975. **12.** Mann, J.L.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J.J.; Nora, A.H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291* (14):697-700, Oct. 3, 1974.

3/76

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

COMMUNICATIONS IN BRIEF

This section is suitable for reporting cases, results of therapeutic trials, and descriptions of new procedures or instruments. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Listeriosis during pregnancy

YONG HYEN HWANG, M.D., F.A.C.O.G.

Department of Obstetrics and Gynecology, Peninsula General Hospital, Salisbury, Maryland

THE FIRST PUBLISHED cases of listeriosis of infancy were recognized during autopsies which were performed on stillborn infants or infants dying within the first few days of life. The picture presented was a uniform one, with disseminated, miliary granulomas or necrosis in all of the organs, particularly in the liver. Subsequently, it became an obvious infection in the fetus. Presumably, depending mainly on the time of infection, it may be revealed by early abortion, late abortion, stillbirth, or the birth of a live infant who, in the course of the first month of life, develops signs of listeriosis by either septicemia or infection in the central nervous system.

Symptoms in the mother are often difficult to evaluate. This is, no doubt, often due to a urinary tract infection or other intercurrent diseases. Septicemia or fever of a short duration sometimes is recorded during or immediately following the abortion or delivery. Usually, the fever ceases after evacuation of the uterus.

C. W., a 17-year-old white girl, gravida 2, para 0, abortus 1, had had a spontaneous abortion 4 months previously, in February, 1974. The last menstrual period began on March 7, 1974 (28 weeks' gestation by dates).

The patient was admitted to the Gynecology Service of Peninsula General Hospital, Salisbury, Maryland, on May 19, 1975, because of high fever, headache, nausea, and vomiting of 2 days' duration. She had one loose bowel movement on admission. She denied any previous illness in the past, with the exception of the usual childhood diseases, and there had been no previous surgery. The personal and social history was unremarkable and the family history was uncontributory.

Reprint requests: Yong Hyen Hwang, M.D., Department of Obstetrics and Gynecology, Peninsula General Hospital, Salisbury, Maryland 21801.

Table I. Laboratory data

Date	*WBC*	*HG*	*HCT*	*RBC*	*MCV*	*Diff. count*		
						Band	*Segs.*	*Lymph.*
5/19/75	7.0	11.8	34.5	3.76	92	4	81	15
5/20/75	10.2	11.0	32.7	3.65	90	4	79	17

STS, negative.
UCG, positive.
Cold agglutination, negative.
Electrolyte, within normal limits.
SMA, 12 within normal limits.
Blood type and Rh, O negative.
Urinalysis, normal.
Coombs test for Rh, negative.
Cervical culture, normal flora.
Throat culture, normal flora.
Daily blood culture, 3 times, were all *Listeriosis monocytogenes* (type 1B reported by CDC).

Systemic review recorded the following: a high fever for 2 days; good appetite, in general, a moderately developed, well-nourished person. ENT, negative; breast, soft, no mass; heart; RSR, no murmur; lungs, clear; abdomen, soft, not palpable; LKS, no tenderness; height of fundus, 18 weeks' size; no fetal heart sounds by fetoscope and Doppler; extremities, negative; rectal examination, negative; neurologic examination, within normal limits.

After admission, the patient was treated conservatively with intravenous fluids, Bendectin, and bed rest, with the diagnosis of intrauterine pregnancy, 28 weeks' gestation by dates, 18 weeks by examination, intrauterine death, and fever of unknown etiology.

Two days after admission, she spontaneously aborted a macerated fetus (17 cm. in length) and placenta complete and intact. The temperature then returned to normal. One day after the abortion, the blood culture was reported as *Listeriosis monocytogenes*, which was sensitive to all antibiotics.

Aqueous penicillin, 500,000 U. every 4 hours, was given for 3 days. She had Rhogam. On May 26, 1975, she was discharged in good condition. The discharge medication was penicillin K, 500 mg. 4 times a day, for 1 week.

The husband's semen was obtained for smear and culture on June 9, 1975 and reported as showing coagulase-negative staphylococci.

Follow-up cervical culture on June 4, 1975, showed *Candida albicans.*

Laboratory data are summarized in Table I.

REFERENCE

1. Scand. J. Microbiol. Pathol. 95-99, 1972.

Pelvic inflammatory pseudotumor: A case report

PRAVIT KUNAKEMAKORN, M.D.
GORDON ONTAI, M.D.*
HOWARD BALIN, M.D.

Department of Obstetrics and Gynecology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

IN 1916, Schlagenhoufer first described a condition characterized by a segmental or diffuse replacement of renal parenchyma which had already been damaged by chronic pyelonephritis by lipid-containing macrophages (foam cells) and occasionally multinucleated giant cells within an area of granulomatous pyelonephritis reaction. This condition was named xanthogranulomatous pyelonephritis.[1] In 1939, Brunn also described this lesion in the lung and a few subsequent cases have been reported following this initial observation.[2] The condition was called xanthoma of the lung, or postinflammatory pseudotumor of the lung. We present a case of postinflammatory pseudotumor condition which occurred as a sequela of chronic pelvic infection. This is the first case we believe to be reported of this condition in the pelvic area.

T. W., a 26-year-old Hawaiian-Caucasian woman, gravida 4, para 4, was admitted to the hospital because of persistent lower abdominal pain and a fever of about 1 week's duration. Approximately 1 week prior to this admission, the patient was seen in the gynecologic outpatient clinic because of low abdominal pain and a history of fever up to 102° F. Examination showed a temperature of 100° F., tender lower abdomen, and an irregularly enlarged uterus of about 6 to 8 weeks' gestational size, firm and tender. Pelvic inflammatory disease with possible fibroid uterus was diagnosed and 500 mg. of polycillin were given orally every 6 hours. On the day of admission, the patient still complained of lower abdominal pain, the temperature was 100° F., and pelvic examination showed a uterus of about 12 weeks' gestational size with marked irregularities, tender, fixed into the posterior cul-de-sac, and extending to the left adnexa area. In the hospital, the patient was given Keflex for 2 days but failed to respond. The pelvic mass, in fact, seemed to be getting larger, more tender, and very firm; she was therefore changed from Keflex to Keflin, 1 Gm. intravenously every 8 hours. The patient responded well. On re-evaluation, the pain had subsided but the mass persisted. It was felt, because of the failure of the antibiotic therapy to decrease the size of the pelvic mass, that exploratory laparotomy was in order. Our differential diagnosis included chronic pelvic inflammatory disease with tubo-ovarian abscess on the left side with a possible concomitant degenerated fibroid of the uterus. Laboratory findings prior to surgery were all within normal limits, including a negative intravenous pyelogram. At operation, it was found that the uterus was normal in size and anteverted, but the left ovary and tube were fused into a large yellowish tissue mass which extended from the anterior surface of the uterus, involving the left side of the broad ligament. It was also attached to the bladder wall and the large bowel. The right tube and ovary, interestingly, appeared normal in appearance. Frozen sections were performed, and the pathology report was "inflammatory pseudotumor, vs. malignancy." Total abdominal hysterectomy and bilateral salpingo-oophorectomy were done with removal of as much of the mass as possible. The postoperative course was uneventful. The histopathologic report was xanthogranulomatous inflammatory reaction of serosa of the uterus and left oviduct. The inflammatory reaction was described as diffuse, including numerous foam cells, histiocytes, lymphocytes, and plasma cells, accompanied by variable numbers of neutrophil leukocytes and erythrocytes (see Fig. 1).

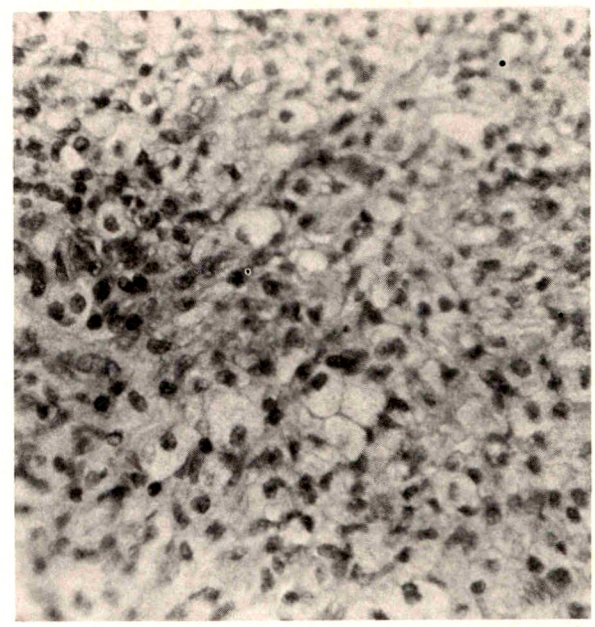


Fig. 1. Numerous lipid-laden macrophages (xanthoid cells) and a lesser number of mononuclear cells, predominantly lymphocytes, scattered throughout the section.

Reprint requests: Pravit Kunakemakorn, M.D., Shasta General Hospital, 2630 Hospital Lane, Redding, California 96001.

*Department of Obstetrics and Gynecology, Kaiser Medical Center, Honolulu, Hawaii 96815.

This patient, who proved to have a postinflammatory reaction of the uterus and adnexa, had microscopic reports that caused true concern on frozen section because of the possibility of a true neoplastic lesion.

Many cases have been reported pertinent to the kidney under the name of xanthogranulomatous pyelonephritis and in the lung as inflammatory pseudotumor. Several other names have also been given to this condition including xanthomas, fibroxanthomas, histiocytes, sclerosing hemagiomas, pseudotumors, and postinflammatory pseudotumor. In these past reports, there was always a history of chronic supperative infection of the affected organ with a mass found afterward which was nonresponsive to therapy. Although its exact etiology is unknown, several possible factors have been suggested such as (1) ineffective or nonappropriate antibiotic therapy, (2) a specific offending but as yet undefined bacterial infection, or (3) an abnormality in lipid metabolism. The clinical course of this condition is benign. The treatment is removal of the affected tissue. Such therapy usually brings with it a good prognosis.

The authors thank Drs. Robert Davis and Walter Levy for their encouragement and assistance and Dr. Paul McCallin for allowing us to present this case.

REFERENCES

1. Rios-Dalenz, J. L., and Peacock, R. C.: Xanthogranulomatous pyelonephritis, Cancer **19:** 289, 1966.
2. Fisher, E. R., and Beyer, F. D.: Post-Inflammatory tumor (xanthoma) of the lung, Dis. Chest **36:** 43, 1959.

Prenatal diagnosis by fetoscopy with subsequent normal delivery: Report of a case

RONALD J. BENZIE, M.D., CH.B., M.R.C.O.G., F.R.C.S.(C)
RALPH M. MALONE, M.B., CH.B., M.R.C.O.G.
MURRAY MISKIN, M.D., F.R.C.S.(C)
NOREEN L. RUDD, M.D., F.R.C.P.(C)
PHILIP A. SCHOFIELD, M.B., CH.B., C.C.F.P.

Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

THE USE OF a fetoscope (the Dyonics Needlescope) which can be introduced percutaneously under local anesthesia has been described by Patrick and associates[1] and ourselves.[2] We now present a patient who had fetoscopy performed at 16 weeks' gestation. Total fetal visualization was achieved and the pregnancy subsequently continued to the delivery of a predicted normal female infant at 39 weeks' gestation.

Reprint requests: Dr. R. J. Benzie, Amniotic Fluid Study Room 104, 4th Floor, Urquhart Wing, Toronto General Hospital, 101 College St., Toronto, Ontario M5G 1L7, Canada.

The patient, a 37-year-old woman, para 3, gravida 4, whose last normal menstrual period by sure dates with a regular cycle was February 29, 1974, was sent for genetic counselling to the Hospital for Sick Children in Toronto on April 16, 1974. The reason for her referral at 6 weeks' gestation in her fourth pregnancy was that her third child, a boy, born 4 years previously, had arthrogryposis multiplex congenita. Her two other children, both girls, were completely normal and there was no history of any congenital abnormality in the family pedigree.

The affected child, aged 4 years, was in the third percentile for height and weight and his head circumference was on the mean. His level of intellectual function appeared normal for his age. The facies were normal; abnormal physical findings were limited to the fixed flexion contractures of his elbows, wrists, fingers, hips, knees, and ankles, with absent flexion creases at antecubital, popliteal, and anterior hip regions. There were no other stigmas which would place him in any of the syndromes of which joint contractures are a part.

The mother was advised that most cases of arthrogryposis multiplex congenita are sporadic. However, because there have been some reported families in which recurrence in siblings appear on an autosomal recessive basis,[3] her empiric risks would be slightly higher than the population at risk for this malformation but still very low.

The patient and her husband, however, appeared in great anxiety about the outcome of this pregnancy and they were both referred to one of us (R. J. B.) for consideration of termination of pregnancy on the grounds of acute anxiety of the mother. At this interview, after the normal history and examination, the suggestion was made by the obstetrician that perhaps fetoscopy might have a role to play in management.

After discussion with the family doctor and again with the mother and her husband, during which the medical and medicolegal aspects were explained, their decision was to go ahead with fetsocopy. They felt that should a fetal skeletal abnormality be seen this would add to the maternal anxiety and constitute strong grounds for termination of the pregnancy.

Ultrasound localization of the placenta was carried out on June 11, 1974. The placenta was posterior fundal and the biparietal diameter was 3.4 cm., compatible with her stated gestation of 16 weeks.

The following morning the patient was admitted as an outpatient to Toronto General Hospital where fetoscopy was carried out in a manner similar to that earlier reported by us.[2]

The fetoscope was inserted under local anesthesia at a point 3 cm. above the pubic symphisis. The amniotic

fluid was noted to be clear. The placenta was seen and its posterior fundal site confirmed. The fetus was seen to be sucking it thumb, an observation we have already recorded.[2] The trunk of the fetus was then seen and appeared normal. The umbilical cord was normal. Next the genitalia, which were noted to be female, were observed, as was the anus. All four limbs were closely scrutinized and all appeared normal. Particular attention was paid to joint movement which in this fetus corresponded to that seen in 65 earlier cases performed in our hospital. No samples of fetal tissue, blood, or amniotic fluid were taken. The fetal back was normal.

When complete fetal visualization had been attained the optic needle and cannula were withdrawn. A small elastoplast bandage was placed over the skin incision. When she had recovered from the diazepam an explanation of the findings was given to the patient and her husband and the decision made to allow this pregnancy to continue normally.

The pregnancy was thereafter managed exactly the same as any other in a patient of this age and parity. Apart from a bout of pyelitis at 24 weeks' gestation, due to *E. coli* infection which was treated successfully with ampicillin therapy, the pregnancy progressed normally.

On November 28, 1974, at 39 weeks' gestation, the patient went into labor and within 1 hour delivered spontaneously by vertex presentation a normal female infant of birth weight 3,260 grams with a 1 minute Apgar score of 8 and a 5 minute score of 9. The third stage was normal. The infant was immediately examined by the neonatologist and pronounced to be normal in all respects. Follow-up examination of the infant at 1 month of age and at 9 months confirmed that she had no abnormality and was progressing normally.

At the present stage of development of fetoscopy we would strongly advise that the technique be applied only to cases such as the one presented, viz., where a previous child has been born with a recognizable and otherwise undiagnosable severe phenotypic abnormality, where the recurrence risk or the maternal anxiety is so great that termination of the pregnancy is thought to be the only reasonable alternative.

Fetoscopy is useful for obtaining samples of fetal blood, skin, or amnion for antenatal genetic diagnosis as we have stated elsewhere.[2] This is the first case, however, in which total fetal visualization, followed by normal delivery, has been attained.

The abortion rate after fetoscopy has still to be established before widespread clinical use can be recommended. We urge that prospective workers in this field obtain experience with the instrument in cases of saline abortion to familiarize themselves with the technique before embarking on clinical cases.

Total fetal visualization must be achieved for the detection of phenotypic abnormalities and we have found that our ability to attain this is improving with experience.

REFERENCES

1. Patrick, J. E., Perry, T. B., and Kinch, R. A. H.: Fetoscopy and fetal blood sampling; A percutaneous approach, Am. J. Obstet. Gynecol. **119:** 539, 1974.
2. Benzie, R. J., and Doran, T. A.: The "fetoscope"—A new clinical tool for prenatal genetic diagnosis, Am. J. Obstet. Gynecol. **121:** 460, 1975.
3. Warkany, J.: Some Syndromes Involving the Extremeties—Arthrogryposis, Chicago, 1971, Year Book Medical Publishers, Inc., pp. 1101-1015.

Ultrasonic measurement of cervical dilatation during labor

FRANS TH. KOK, M.D.
HENK C. S. WALLENBURG, M.D., Ph.D.
JURIY W. WLADIMIROFF, M.D., Ph.D.

Department of Obstetrics and Gynecology, Academisch Ziekenhuis Erasmus Universiteit, Rotterdam, The Netherlands

Several attempts have been made to develop a device for objective measurement of cervical dilatation during labor. The basic design of these instruments (cervimeters) consists of a pair of caliper arms with their distal ends attached to opposing rims of the external cervical os. The distance between the proximal ends will vary proportionally to the changes in width of the cervical os. After calibration, these changes can be measured by multiple readings[1, 2] or continuously recorded by means of an electromechanical system consisting of a

Reprint requests: Dr. Henk C. S. Wallenburg, Department of Obstetrics and Gynecology, AZR-Dijkzigt, Dr. Molewaterplein 40, Rotterdam, The Netherlands.

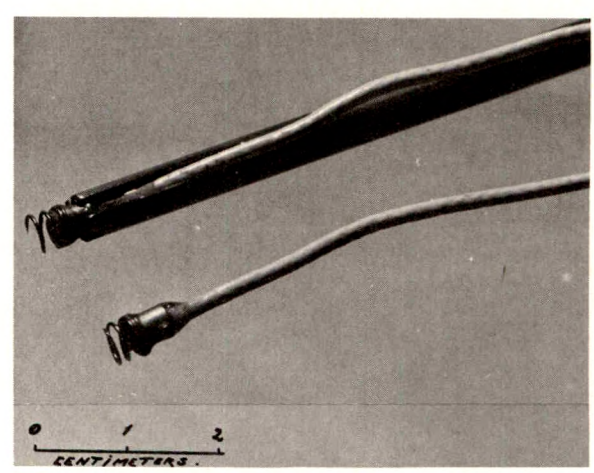


Fig. 1. The two transducers of the ultrasonic cervimeter, with (top) and without (bottom) the guide tube.

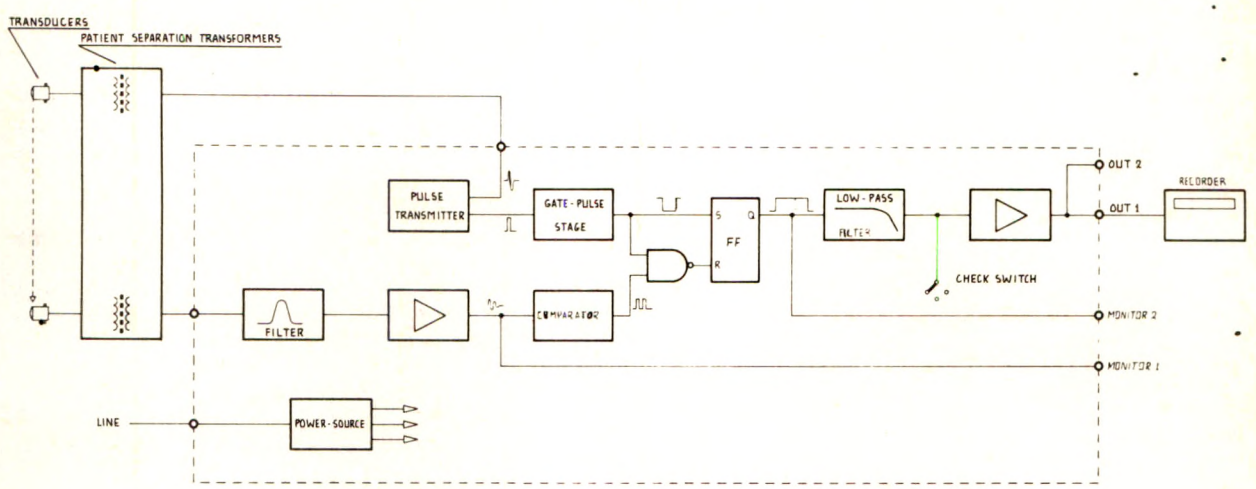


Fig. 2. Block diagram of the electronic part of the ultrasonic cervimeter.

potentiometer and appropriate amplifiers and a graphic recorder.[3–5] The mechanical cervimeters are rather heavy and not very comfortable to the patient. In addition, the fixation of the heavy instrument to the cervix may influence the dilatation pattern, and cervical lacerations have been described.[2, 3] These shortcomings limit the clinical usefulness of the instruments.

In this report a new cervimeter based on the principle of ultrasound is described. This device appears to be suitable for routine clinical application. The intravaginal part of the device consists of two ultrasound transducers, composed of barium titanate, set in stainless steel cylinders with a length of 5 mm., a diameter of 4.5 mm., and a weight of 0.3 Gm. A small steel coil allows each cylinder to be screwed into the rim of the external cervical os by means of a special guide tube (Fig. 1). A long coaxial cable connects both transducers with the electronic part of the instrument, which consists of a pulse transmitter and appropriate filters, amplifiers, and transformers (Fig. 2). The pulse transmitter generates a continuous ultrasound signal with a frequency of 0.6 MHz in one of the transducers. The signal is received by the other transducer, filtered, amplified, and compared with the emitted pulse. The time difference is transformed into centimeters of distance between the two transducers and continuously written on a polygraph. The output can also be recorded on magnetic tape.

The ultrasonic cervimeter has been applied in 20 nulliparous or multiparous patients in the first stage of labor. The patients were prepared for an aseptic vaginal examination in the lithotomy position. Under direct vision by means of a speculum the guide tube with one of the transducers in its tip was introduced into the vagina, directed against the lateral rim of the external cervical os at 3 or 9 o'clock, and the coil was screwed into the tissue. In the same manner the second transducer was attached to the external os opposite to the first one. Intrauterine pressure was measured by means of a transcervical, fluid-filled, open-tip catheter connected to an appropriate pressure transducer, and together with the cervical dilatation written on the same polygraph.

The accuracy in vitro was tested in a medium of water and meat. The maximum error in ultrasonic measurement of the distance between the two transducers in this medium appeared to be no more than 3 mm. over the range from 2 to 10 cm.

The ultrasonic measurements during labor were compared with the results of multiple caliper measurements of the cervical dilatation, made without knowledge of the ultrasonic data. Over the whole range of cervical dilatation the maximum difference between the two sets of data was 4 mm. The instrument appeared to cause no discomfort to the patient and significant trauma to the cervix was never observed.

In most cases a continuous recording of cervical dilatation from 2 to approximately 10 cm. could be obtained. The cervical dilatation could be shown to follow a wave pattern reflecting the intrauterine pressure curve (Fig. 3). Our preliminary observations indicate that during each contraction maximal cervical dilatation concurs with the maximal intensity of the contraction. Before complete effacement of the cervix is reached the os returns almost completely to its previous size when the contraction subsides. After effacement of the cervix the difference between cervical dilatation at the beginning and at the end of each uterine contraction appears to increase when labor progresses. Generally, the curve of cervical dilatation plotted against time shows the sigmoid shape that has been postulated by Friedman.[2, 3]

The ultrasonic cervimeter appears easy to apply, without discomfort to the patient, and allows continuous and accurate measurement of cervical dilatation. Because of their light weight the transducers do not

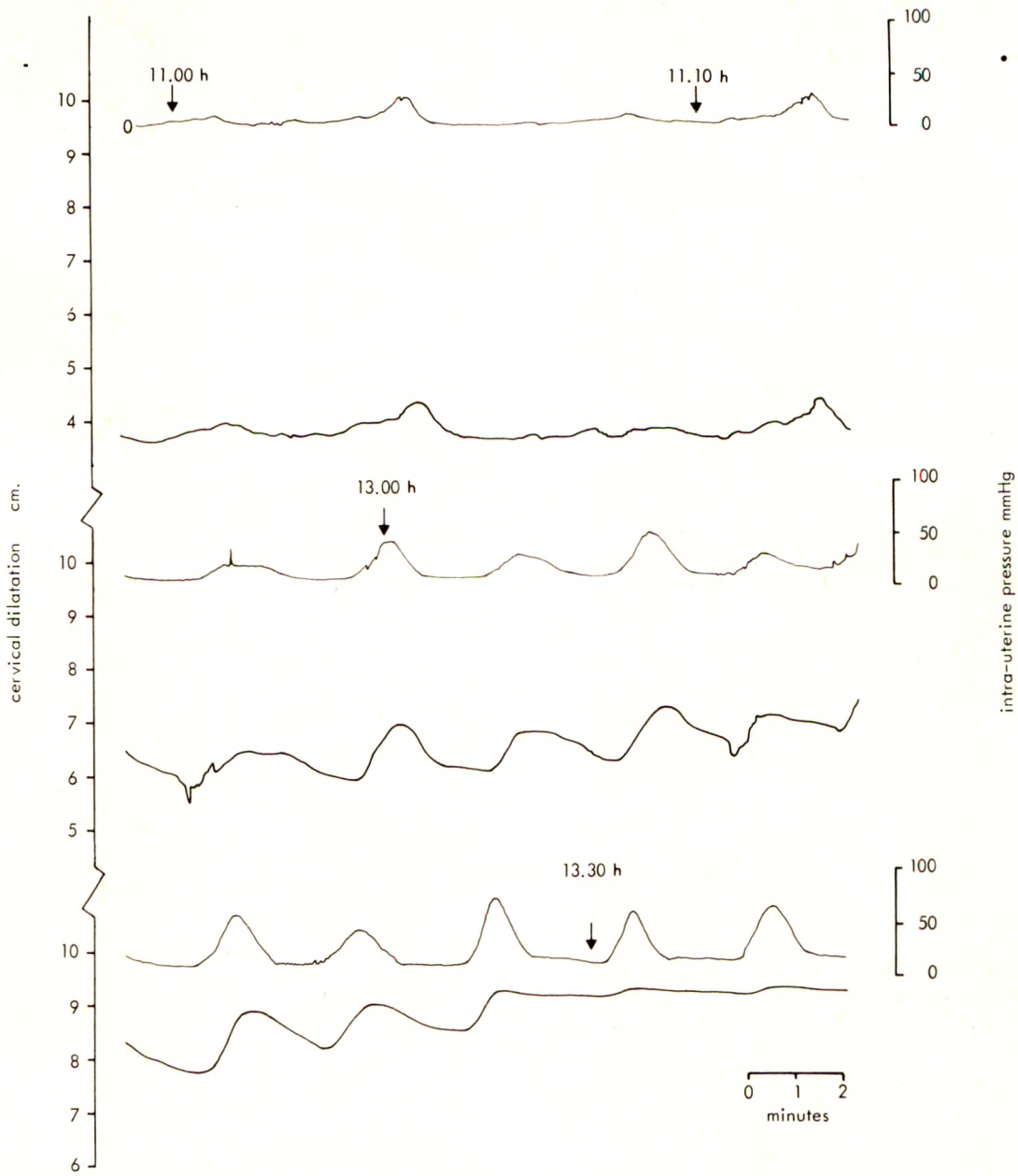


Fig. 3. Simultaneous recording of intrauterine pressure (upper channel) and cervical dilatation (lower channel) during the first stage of labor in a 23-year-old woman, gravida 1, with ruptured membranes. Paper speed 3 cm. per minute. During the recording, cervical dilatation progressed from 3 to 9 cm. The cervical dilatation shows a wave pattern reflecting the intrauterine pressure curve.

distort the normal circular dilatation pattern of the cervix.

Presently, further clinical experimental studies are in progress on cervical dilatation in relation to intrauterine pressure in normal and abnormal labor. These studies could contribute to a better understanding of the dynamics of human labor.

REFERENCES

1. Wolf, W.: Arch. Gynäkol. **180:** 178, 1951.
2. Friedman, E. A.: Am. J. Obstet. Gynecol. **71:** 1189, 1956.
3. Friedman, E. A., and von Micsky, L. I.: Am. J. Obstet. Gynecol. **87:** 789, 1963.
4. Siener, H.: Am. J. Obstet. Gynecol. **86:** 303, 1963.
5. Siener, H.: Geburtshilfe. Frauenheilkd. **32:** 123, 1972.

Antepartum detection of congenital complete fetal heart block: A case report

DAVID H. ARMSTRONG, M.D.
YUJI MURATA, M.D.
CHESTER B. MARTIN, JR., M.D.
TSUYOMU IKENOUE, M.D.

Department of Obstetrics and Gynecology, University of California at Los Angeles, and Department of Obstetrics and Gynecology, Los Angeles County–University of Southern California Medical Center, Los Angeles, California

UNTIL NOW, the presence of complete congenital heart block (CCHB) has been suggested only by antenatal detection of persistent fetal bradycardia. Although two recent reports have established the validity of direct fetal monitoring as a means of diagnosing fetal heart block during labor,[1, 2] no previous report has documented atrioventricular dissociation antenatally.

Reprint requests: Yuji Murata, M.D., LAC-USC Medical Center, Women's Hospital, Room 5K-22, 1240 North Mission Rd., Los Angeles, California 90033.

A 20-year-old primigravida had been observed since the twelfth menstrual week of pregnancy. At 30 menstrual weeks' gestation, fetal bradycardia of 72 beats per minute (b.p.m.) was detected by auscultation. Subsequent fetal heart rate observations were generally about 60 b.p.m. At 36 weeks, simultaneous abdominal fetal electrocardiogram (FECG) and phonocardiogram (PCG) recordings and the abdominal FECG and ultrasound Dopplercardiogram (DCG) recordings were then obtained on magnetic tape for detailed analysis.

The fetal heart rates by DCG and PCG were 130 to 140 and 40 to 50 b.p.m., respectively (Fig. 1). In addition, the fetal DCG exhibited two different types of signals which were interpreted as representing atrial and ventricular movements of the fetal heart. The frequency of the presumed ventricular movements detected by the DCG coincided with the heart rate obtained by the PCG. Two or three atrial movements were observed between consecutive ventricular signals on the DCG. Fetal QRS complexes could not be identified with certainty in the abdominal FECG tracing. A diagnosis of probable second- to third-degree block of the fetal heart was made on the basis of the DCG and PCG records.

Labor began spontaneously at 39 weeks' gestation. Direct FHR monitoring was carried out with a scalp electrode but the FHR record showed a totally irregular signal. A recording of FECG was obtained at the same time through the FHR monitor (Fig. 2). Three different signals were identified according to rate and configuration: maternal QRS complexes

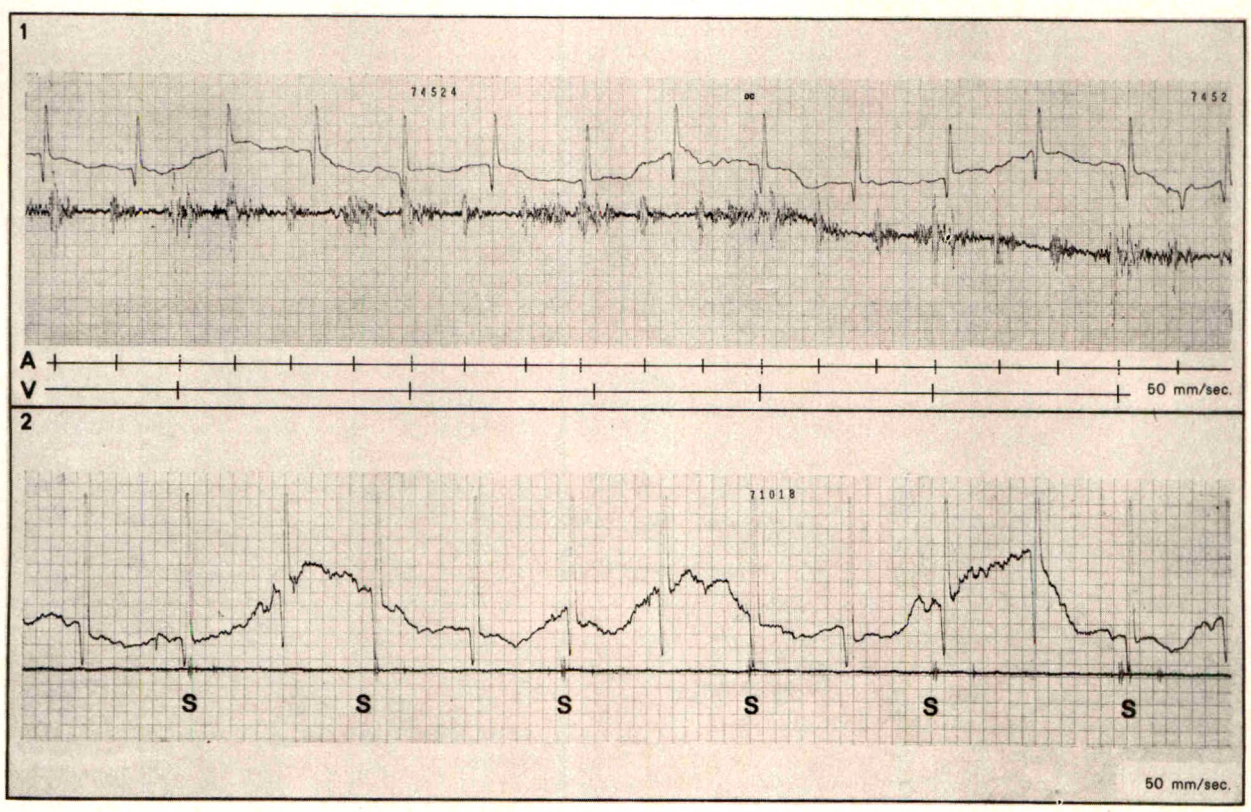


Fig. 1. Simultaneous recording of abdominal fetal ECG and fetal ultrasound Dopplercardiogram *(1)* and abdominal fetal ECG and fetal phonocardiogram *(2)*. The QRS complexes on both ECG tracings represent only maternal signals. *A*, Atrial movement (Doppler); *V*, ventricular movement (Doppler); *S*, heart sound (phonocardiogram).

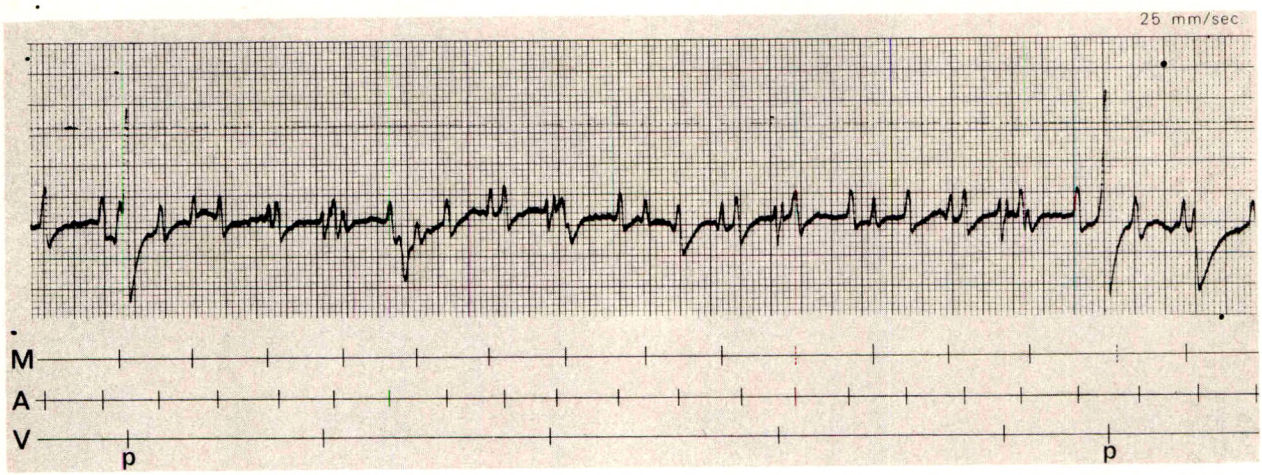


Fig. 2. ECG obtained by direct fetal scalp electrode during labor. *M*, Maternal QRS complex; *A*, fetal atrial signal; *V*, fetal ventricular signal; *P*, fetal premature ventricular contraction.

(116 b.p.m.), fetal atrial signals (165 b.p.m.), and fetal ventricular signals (41 b.p.m.). The diagnosis of third-degree heart block was thus confirmed.

A male infant weighing 3,300 grams was delivered vaginally, with Apgar scores of 6 and 8 at 1 and 5 minutes.

Complete heart block persisted after birth, with additional findings suggesting combined right and left ventricular hypertrophy and right atrial enlargement. The ventricular rate was 40 b.p.m. Slight cyanosis was observed, but no other abnormalities were noted. Cyanosis persisted and, at age 21 hours, a cardiac pacemaker was inserted. Thereafter, the heart rate ranged between 110 and 120 b.p.m. Despite the properly functioning pacemaker and assisted respiration, the infant died at 28 hours of age. Death was preceded by return of cyanosis and, ultimately, respiratory arrest. Postmortem examination revealed right atrial and ventricular dilatation with mild muscular hypertrophy and functional tricuspid and pulmonic valvular insufficiency, widely patient ductus arteriosus, aspiration of amniotic fluid with early bronchopneumonia, and passive congestion of viscera. No congenital anatomic heart lesion was found. Special histologic stains of the His bundle revealed no abnormalities. The postmortem findings are probably the result of hemodynamic changes and the cause of the heart block remains unknown.

The differential diagnosis of fetal bradycardia is of practical importance, for management varies depending upon whether the slow rate is a manifestation of fetal distress or represents heart block. In the case of CCHB detected antenatally, appropriate arrangements can be made in advance of delivery to evaluate and, if necessary, to treat the infant immediately following birth. The case reported here demonstrates that CCHB can be diagnosed before labor by means of Doppler and phonocardiography to detect discordant atrial and ventricular rates. CCHB should be suspected when the stethoscope and Doppler fetal pulse detection reveal widely differing heart rates.

REFERENCES

1. Sokol, R. J., Hutchinson, P., Krouskop, R. W., et al.: Congenital complete heart block diagnosed during intrauterine fetal monitoring, Am. J. Obstet. Gynecol. **120:** 1115, 1974.
2. Anderson, G. G., and Hanson, T. M.: Chronic fetal bradycardia, Obstet. Gynecol. **44:** 896, 1974.

Rectouterine fistula associated with the Cu-7 intrauterine contraceptive device

R. D. PATCHELL, M.D.

Department of Obstetrics and Gynecology, West Virginia University Medical Center, Charleston Division, Charleston, West Virginia

Endoectocervical fistula production by the copper-bearing limb of a malpositioned intrauterine contraceptive device, (IUD) has been reported by Rienprayina and associates[1] and Cederqvist and Fuchs.[2] Each group reported an additional case of posterior perforation with the device removed through a posterior colpotomy. Reports[3, 4] indicate that the intraperitoneal copper-bearing device causes a more intense reaction than the non–copper-bearing IUD. Rapid envelopment by omentum may protect the bowel but laparotomy may be necessary for removal. The following case suggests that the malpositioned Cu-7 may cause rectouterine fistula formation.

A 34-year-old woman, gravida 3, para 3, was investigated at a diagnostic clinic in April, 1975, because of "stomach problems" of six months' duration. Barium enema studies were interpreted as showing a rectovaginal fistula. She was immediately referred for gynecologic evaluation and management.

This overweight woman had experienced vague upper abdominal pains for many years. In March, 1974, she had

Reprint requests: Dr. R. D. Patchell, Department of Obstetrics and Gynecology, Memorial Division, Charleston Area Medical Center, Charleston, West Virginia 25304.

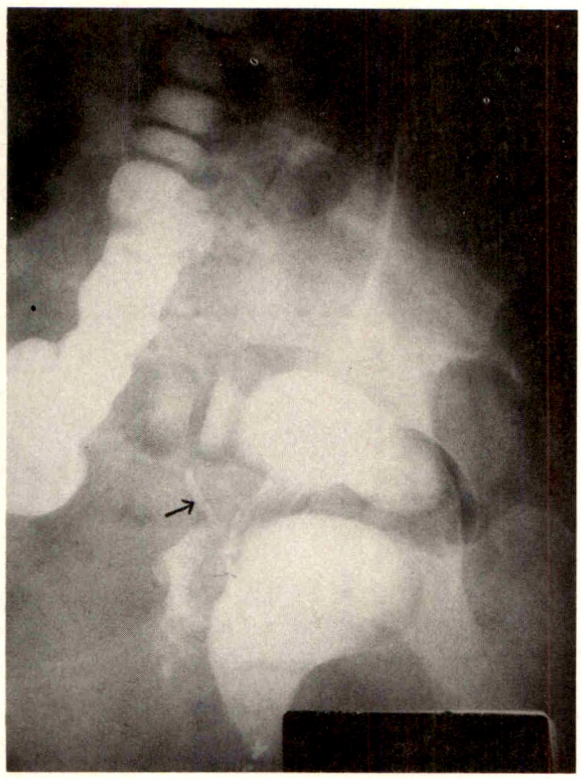


Fig. 1. Barium enema showing the misplaced IUD anterior to the rectum with barium visualized in the vagina.

gastrointestinal, barium enema, and sigmoidoscopic examinations. No abnormalities were noted. She was advised to reduce and to discontinue oral contraceptive medication. At that time, a Cu-7 IUD was inserted without difficulty by an experienced gynecologist. In October, 1974, a new pattern of abdominal pain and a change in bowel habits gradually occurred. At intervals of seven to 10 days, she had episodes of lower abdominal cramps with stools becoming hard and pelletlike. After two or three days, the pain ceased and bowel movements became loose. On several occasions she noticed a foul brown vaginal discharge. The menstruation pattern was unchanged.

Examination revealed an IUD string and a small portion of an IUD at the external os. Definite thickening and slight tenderness of the cul-de-sac were noticed. Examination revealed no evidence of a rectovaginal fistula. Sigmoidoscopy to 20 cm. revealed no abnormalities. She was afebrile. Review of the barium enema studies revealed extraluminal barium anterior to the rectum and extending into the vagina. An intrauterine device was visible with the copper-bearing limb projecting into the collection of extraluminal barium (Fig. 1). The patient stated that following the barium enema she passed barium through the vagina.

A presumptive diagnosis of rectouterine fistula secondary to a malpositioned Cu-7 was made. The device was removed without difficulty. Spontaneous closure was anticipated, and hysterography was considered to be contraindicated. She was advised to keep an accurate temperature record and to report immediately if any fever or increased pain occurred. On two occasions following the removal of the Cu-7, she passed gas from the vagina. During the following six weeks, the pain and intermittent constipation gradually ceased. Hysterography, barium enema, and sigmoidoscopy were then performed. No evidence of the previously demonstrated abnormality was noted. No leakage of bowel content into the vagina was demonstrated by enteric dye and vaginal tampon testing. She has remained afebrile. The cul-de-sac thickening and tenderness are now absent.

It is unlikely that the omentum in this obese lady would reach to the cul-de-sac. Thus, protective envelopment of the device might not have occurred. The sequence of a normal lower bowel study, subsequent demonstration of a rectogenital fistula, and failure to demonstrate any abnormality six weeks after removal of the device would strongly suggest a cause-and-effect relationship. The complete subsidence of symptomatology following the removal of the device substantiates this.

Although perforation by an IUD is an uncommon occurrence, the possibility should be considered in any wearer who develops abdominal pain or intestinal tract symptomatology.

REFERENCES

1. Rienprayina, D., Phaovausasi, S., and Somboonsuk, A.: Cervical perforation by the copper T intrauterine device, Contraception **7:** 515, 1973.
2. Cederqvist, L., and Fuchs, F.: Cervical perforation by a copper T intrauterine device, Am. J. Obstet. Gynecol. **119:** 854, 1974.
3. Tatum, H. J.: Metallic copper as an intrauterine contraceptive agent, Am. J. Obstet. Gynecol. **117:** 602, 1973.
4. Newton, J., Elias, J., McEwen, J., and Mann, G.: Intrauterine contraception with the copper T: Evaluation after two years, Br. Med. J. **17:** 447, 1974.

Ultrasound localization of laminaria

TIMOTHY G. LEE, M.D.
DONALD C. BARNETT, M.D.

Diagnostic Radiology, Division of Ultrasound, School of Medicine, University of Oregon Health Sciences Center, Portland, Oregon

The use of ultrasound B-mode scanning in the localization of intrauterine contraceptives has been well established and previously reported.[1–3] To our knowledge, use of ultrasound for localization of laminaria and detection of a displaced laminaria has not been reported. With increased social acceptance of abortions and the reintroduction of *Laminaria digitata* to accomplish abortions,[4] ultrasound localization of laminaria may become increasingly important. Laminaria also has been used in intracavitary application for

Reprint requests: Dr. Timothy G. Lee, Diagnostic Radiology, Division of Ultrasound, University of Oregon Health Sciences Center, School of Medicine, Portland, Oregon 97201.

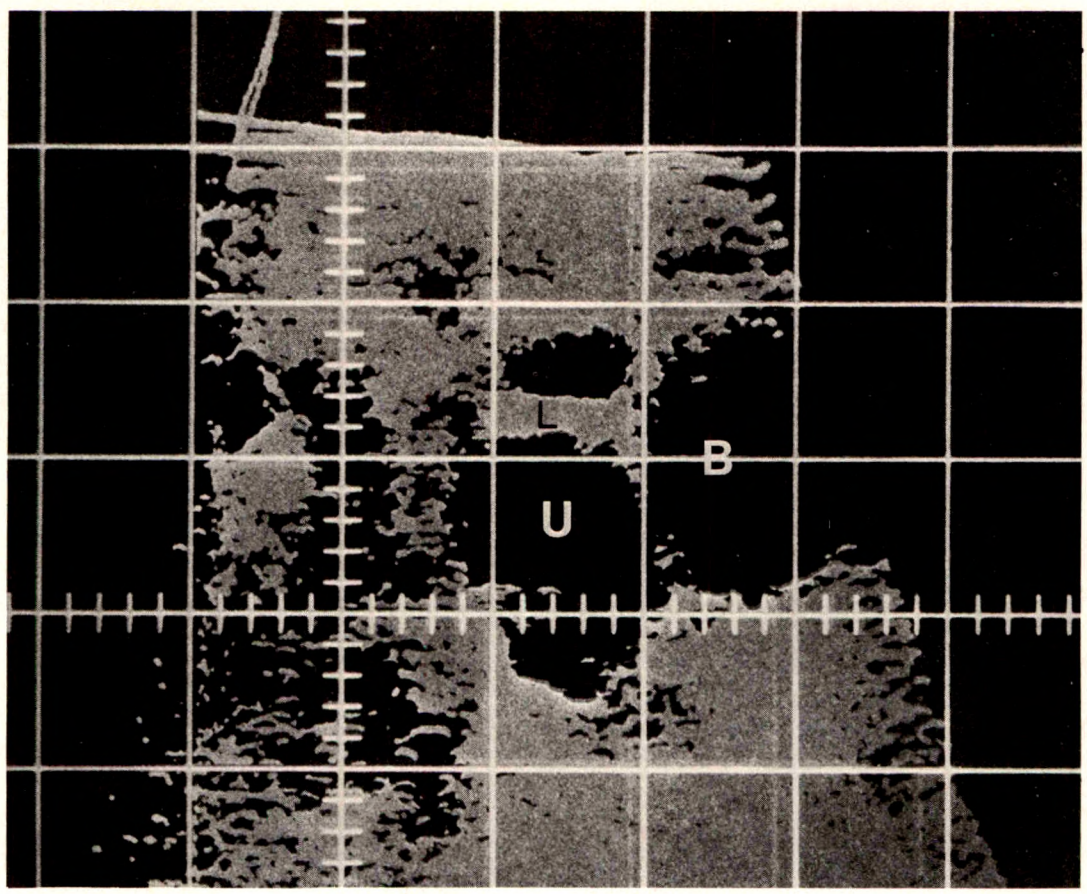


Fig. 1A. Longitudinal scan, pelvis. The characteristic echo of the laminaria *(L)* is seen in the cavity of the uterus *(U)* rather than in the proper cervical canal location. Bladder *(B)*.

carcinoma of the cervix.[5] There are other uses of laminaria.[4]

The purpose of this paper is to illustrate ultrasound localization of laminaria in vivo and in vitro. A displaced laminaria in a patient (thought to have expelled the laminaria by accident) was correctly localized by ultrasound.

The principles and technique of ultrasound B-mode scanning have been previously reported.[6–8] We obtained a surgically removed uterus and scanned it in the water bath with and without the laminaria inserted in the cervical canal. Our findings show that laminaria can be clearly identified, showing a characteristic solid rodlike appearance of accurate dimension in the cervical canal.

A pelvic scan of a patient with laminaria inserted prior to abortion showed the laminaria correctly located in the cervical canal. This was confirmed later at abortion.

A patient admitted with a diagnosis of endometritis had a laminaria inserted to facilitate drainage. It was missing at the time of a subsequent physical examination, and thought to have been expelled accidentally. An ultrasound B-scan was requested and showed the laminaria to be contained within the uterus (Fig. 1). This was later removed by dilatation and curettage.

To our knowledge, this is the first reported case of laminaria localization by ultrasound. With the reintroduction of *Laminaria digitata* and increased frequency of its use, its dislocation may become a potential problem. B-mode ultrasound scanning can accurately locate the position of the laminaria. Our study also suggests that ultrasound may be used in the localization of nonradiopaque intrauterine foreign bodies.

REFERENCES

1. Cochrane, W. J., and Thomas, M. A.: The use of ultrasound B-mode scanning in the localization of intrauterine contraceptive devices, Radiology **104:** 623, 1972.
2. Iannіruberto, A., Mastroberardino, A.: Ultrasonic localization of the Lippes loop, Am. J. Obstet. Gynecol. **114:** 78, 1972.
3. Nemes, G., and Kerenyi, T. D.: Ultrasonic localization of

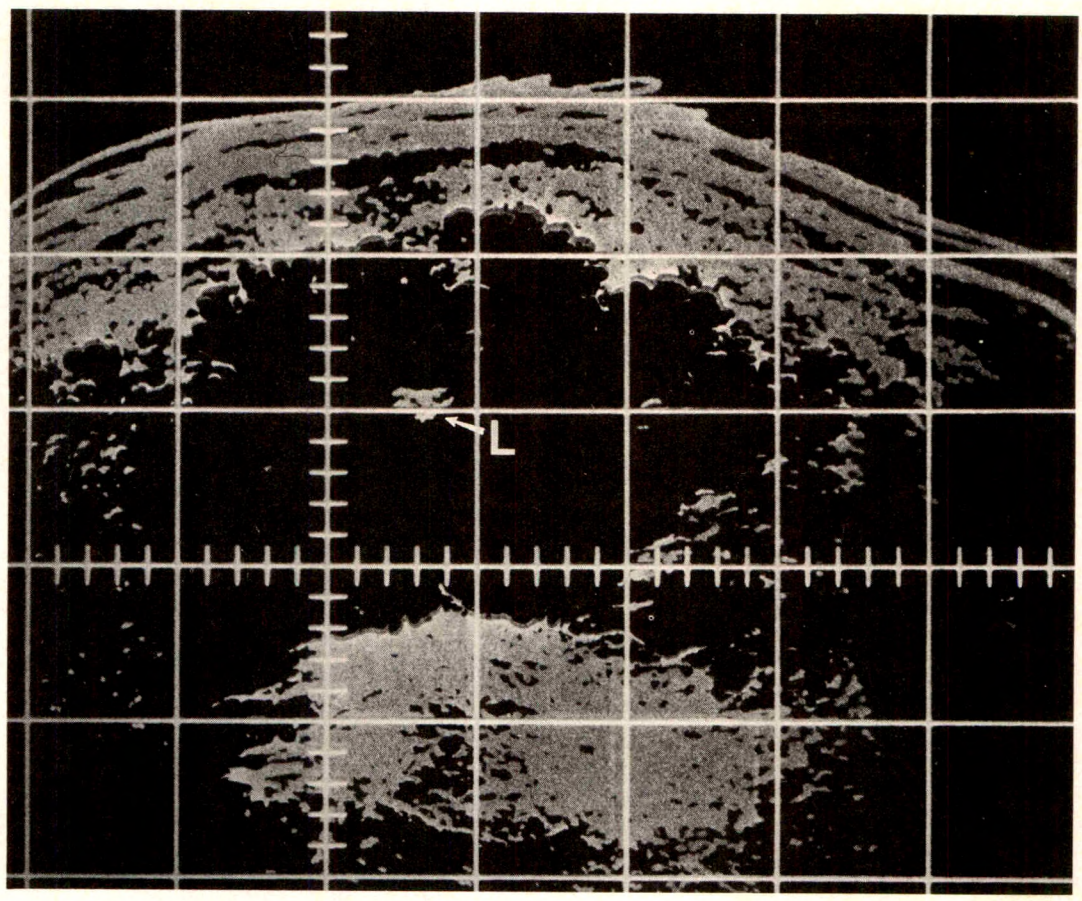


Fig. 1B. Transverse scan, pelvis.

the IUCD—a new technique, AM. J. OBSTET. GYNECOL. **109:** 1219, 1971.
4. Newton, B. W.: Laminaria tent: Relic of the past or modern medical device? AM. J. OBSTET. GYNECOL. **113:** 442, 1972.
5. Ferree, C. R., Raben, M., and Linton, E.: Use of laminaria in intracavitary applications for carcinoma of the cervix, Radiology **109:** 222, 1973.
6. Donald, I.: Ultrasonic echo sounding in obstetrical and gynecological diagnosis, AM. J. OBSTET. GYNECOL. **93:** 935, 1965.
7. Kohorn, E. I., Morrison, J., and Ashford, C.: Ultrasonic scanning in obstetrics and gynecology, Obstet. Gynecol. **34:** 515, 1969.
8. Thompson, H. E.: Clinical use of pulsed echo ultrasound in obstetrics and gynecology, Obstet. Gynecol. Surv. **23:** 903, 1968.

Erratum

In the May 1, 1976, issue of the JOURNAL, in the article entitled, "Impact of cephalosporin prophylaxis on conization–vaginal hysterectomy morbidity," by John P. Forney, M.D., C. Paul Morrow, M.D., Duane E. Townsend, M.D., and Philip J. Disaia, M.D., on page 102, in Table I, under the column heading "Postoperative temperature morbidity definition," the data of "Ledger and co-workers[4]" which read "100.4° F. or greater for 2 days, exclusive of first 48 hours" should have been "100.4° F. or greater for 2 days, exclusive of first 24 hours."

CORRESPONDENCE

Diazoxide in treatment of severe pre-eclampsia and hypertensive encephalopathy

To the Editors:

In recent publications, the potential use of diazoxide* has been promoted as the drug of choice for severe hypertensive manifestations of toxemia of pregnancy. This drug has been found enormously effective in the treatment of malignant hypertension and, in fact, is currently considered the drug of choice for crises of this nature. In a recent article, Finnerty[1] proposes, in essence, that the drug be considered the medication of choice for the treatment of severe pre-eclampsia and hypertensive encephalopathy. The fusion of these two entities into one indication is highly regrettable. Although encephalopathy may indeed supervene in neglected "toxemia," it is rare that such a development may not be adequately treated by safer measures, particularly for the fetus.

Objections to the use of diazoxide include, by the authors's own statement, that the medication reduces renal blood flow, a circumstance commonly presumed to be associated with coincident reduction of uterine blood flow; such a condition is to be abhorred in an already precarious state. Despite the encouraging claims of its use in human subjects,[2, 3] it has been demonstrated with intensive use in laboratory animals to cause extensive pancreatic and, in some cases, peripheral muscle destruction.[4] The author notes also the well-recognized tendency for the drug to produce hyperglycemia, limiting its use, at least in patients with unstable diabetes mellitus. The author proposes the use of furosemide to counteract the obligatory reduction in renal blood flow and to maintain adequate urinary output. Furosemide is specifically considered by the manufacturer to be contraindicated in pregnancy except under extreme circumstances.[5] This is not to say that the circumstances surrounding hypertensive crisis in pregnancy may not be extreme, but the potential fetal toxicity of some medications when used at times when other measures would be adequate seems highly ill-advised. Poisoning the renal tubular mechanisms for the sake of maintaining adequate urinary output should be restricted to incipient renal failure, a development to which the "toxemic" patient may be predisposed, but also a condition to which she should not be predisposed by therapy.

The author also proposes the use of tolbutamide as a possible remedy for the hyperglycemia noted in the mother (and in laboratory fetuses). Tolbutamide is considered by most perinatologists as relatively contraindicated in pregnancy due to its well-known potential to produce unstable glucose-insulin homeostasis in the fetus. Until such time as investigators can satisfy perinatal specialists that the long term follow-up of infants exposed to diazoxide as fetuses does not ultimately result in late-developing evidence of pancreatic islet cell insufficiency or other more immediate complications, the drug should not, in the opinion of this author, be used except in conscientiously conducted research. Is it not possible that the absence of neonatal hypoglycemia, even in growth-retarded infants in whom such events are common, may be the result of partial islet cell destruction and renal suppression, limiting the ability to mobilize and distribute glucose stores at a normal rate? It is the responsibility of responsible perinatal specialists to prevent this disaster in the future.

Others, as yet unquantitated, risks of diazoxide therapy also need to be investigated.[6] The drug has been associated with a high incidence of arrest of uterine contractions. Some even propose its use for this purpose.[7] Severe but reversible hypotension can occur; potassium, chloride, bicarbonate, and uric acid excretion is reduced. The combination of diazoxide and furosemide can result in a marked decrease in extracellular fluid volume, and patients are generally advised to avoid the upright posture for eight to 10 hours following its administration. This potential effect is unthinkable in the severely volume-depleted, typical patient with severe pre-eclampsia. Diazoxide decreases cortisol excretion to minimal levels after 200 to 400 mg. daily. Diazoxide in children has been reported to decrease immunoglobulin G production and the mitotic response to phytohemagglutinin at markedly elevated doses in vitro. Diazoxide is reversibly bound to albumin and might be a factor in displacement of bilirubin from albumin-binding sites in the fetus. Transient cerebral or myocardial ischemia with hypotension has been reported. Neutropenia, thrombocytopenia, and eosinophilia (related to transient adrenal insufficiency?) have been reported with diazoxide, although these effects are reversible. Finally, the use of tolbutamide in dogs has been shown to reverse the hypoglycemic effect of diazoxide but also to reverse the hypotensive and antidiuretic effects as well. This seems potentially to mitigate against the effective use of tolbutamide to antagonize the unwanted side

*Hyperstat, Schering Corp., 1011 Morris Ave., Union, New Jersey 07083.

effects, removing one of the proponents' proposed safeguards against hyperglycemia. Hyperosmolar nonketotic coma has been associated with diazoxide therapy for hypoglycemia in one child.[8]

All things considered, it would seem that the enthusiastic use of diazoxide in severe "toxemia" cannot be supported except as a research tool, with informed consent on the part of the patient and prolonged and conscientious follow-up of the newborn infant. With modern premature intensive care capabilities, it would seem that using a drug with all of the above-cited potential risks is not yet justified except in the most dire of circumstances.

Richard P. Perkins, M.D.
Department of Obstetrics and Gynecology
University of Colorado Medical Center
4200 East 9th Avenue
Box B198
Denver, Colorado 80220

REFERENCES

1. Finnerty, F. A.: Management of hypertension in toxemia of pregnancy, Hosp. Med. **11:** 52, 1975.
2. Michael, C. A.: The control of hypertension in labour, Aust. N. Z. J. Obstet. Gynaecol. **12:** 48, 1972.
3. Pohl, J. E. F., Thurston, H., Davis, D., and Morgan, M. Y.: Successful use of oral diazoxide in the treatment of severe toxemia of pregnancy, Br. Med. J. **2:** 568, 1972.
4. Boulos, B. M., Davis, L. E., Almond, C. H., and Jackson, R. L.: Placental transfer of diazoxide and its hazardous effect on the newborn, J. Clin. Pharmacol. **11:** 206, 1971.
5. Product information brochure, Lasix (furosemide), Hoechst Pharmaceuticals, Inc.
6. Symposium on diazoxide, Drugs **2:** 73, 1971.
7. Landesman, R., DeSousa, F. J. A., Coutinho, E. M., Wilson, K. H., and DeSousa, F. M. B.: Inhibitory effect of diazoxide in normal term labor, AM. J. OBSTET. GYNECOL. **103:** 430, 1969.
8. Balsam, M. F., Baker, L., and Kaye, R.: Hyperosmolar nonketotic coma associated with diazoxide therapy for hypoglycemia, J. Pediatr. **78:** 523, 1971.

Sudden fetal death during monitored labor

To the Editors:

I read with great interest the "Communication in brief," "Unforeseen sudden intrapartum fetal death in a monitored labor," by Drs. Hayashi and Fox (AM. J. OBSTET. GYNECOL. 122: 786, 1975.

The authors claim that there was no ominous fetal heart rate (FHR) pattern and that retrospective analysis of the tracings revealed a short-term, beat-to-beat variation but a conspicuous absence of long-term periodic variation. In addition, they failed to find a narrowed oscillation (sinusoidal FHR) pattern which may be associated with fetal compromise.

I submit that the monitor tracings did indeed indicate a compromised fetal status and were not normal or reassuring and that the failure to fully recognize the true nature of the FHR pattern was mainly due to the limitations of the particular fetal monitor utilized and the slow (1 cm. per minute) paper speed recording.

Unfortunately, there is a total lack of standardization in fetal monitoring system (FMS) strip-chart displays produced by various manufacturers. Paul[1] has shown that by altering the vertical scaling and changing the horizontal paper speed the FHR–uterine contraction patterns can be dramatically altered. For example, type I dips (Caldeyro-Barcia) may refer to both early and variable decelerations (Hon), but Hon was able to make this distinction because of a display technique which utilized a 3 cm. per minute paper speed and vertical scaling of FHR = 30 beats per centimeter, as opposed to a 1 cm. per minute paper speed and vertical scaling of FHR = 20 beats per centimeter (Caldeyro-Barcia).

In the case report, a Hewlett-Packard FMS with a paper speed of 1 cm. per minute and vertical scaling of FHR = 20 beats per centimeter was used, and this led to difficulty in fully intepreting the data present.

At our institution, in the past year, we have had two similar experiences at a 1 cm. per minute paper speed, resulting in babies with low Apgar scores, one of whom died neonatally. In each case close review of the records indicated late deceleration that would have been more clearly interpretable if the machine had been speeded to 3 cm. per minute. As a result, we now run our monitors at 3 cm. per minute on all patients in active labor.

The authors describe short-term, beat-to-beat variation but do not indicate whether they thought this was diminished, average, or increased beat-to-beat variability. It is apparent to me that the base-line FHR is rather fixed (at about 150) and there are subtle changes suggestive of late deceleration in the tracings in Figs. 2A to 2C. I submit that an instrumentation display at 3 cm. per minute paper speed and vertical scaling of FHR = 30 beats per centimeter (as in the Corometrics* or Berkeley† FMS) would have clearly indicated markedly reduced beat-to-beat variability and mild late deceleration (<15 beats per minute [BPM]—Hon) in tracings A to C.

In Fig. 2D, the subtle changes suggestive of late deceleration seen in Figs. 2A to 2C are not apparent, and this may be related to a reduction in the frequency of uterine activity representing less stress. In addition, the FHR in Fig. 2D shows an increase in the number of upward and downward vertical deflections. These may represent either electrical "noise" or possibly fetal beat-to-beat arrhythmia with premature ventricular contractions and sinus arrest. To distinguish between "noise" and arrhythmia would require a simultaneous fetal electrocardiographic recording.[2]

The last portion of Fig. 2D raises some unanswered and possibly unanswerable questions. The authors indicate that following a vaginal examination the FHR suddenly dropped from 150 to 86 BPM and that a

*Corometrics Medical Systems, Inc., 2 Barnes Industrial Park Rd., Wallingford, Connecticut 06492.

†Berkeley Scientific Labs., 2332 Fourth St., Berkeley, California 94710.

second electrode was placed which revealed an identical rate (an identical recording or a "clean" tracing?) synchronous with the maternal pulse. The tracing following the application of the second electrode is not presented but, if identical to the tracing in Fig. 2D, can be interpreted only as "noise" as the automatic gain control (AGC) of the FMS searches for a recordable signal. This cannot be interpreted as representing maternal cardiac activity recorded through the electrode and differs markedly from the tracings reported in the author's own Reference No. 5. It also cannot be interpreted to represent fetal death, as it is simply a loss of recordable signal.

It is not clear from the case report at what point the Doptone was used (in relation to Fig. 2D) to search for the fetal heartbeat in this obese patient (234 pounds). It is possible that the fetal monitor malfunctioned (last segment of Fig. 2D) and that the fetus was actually alive during the "noisy" segment of Fig. 2D. A second monitor or a new leg plate might have given an interpretable recording. It is also possible, though not likely or provable, that a beat-to-beat arrhythmia (sinus arrest) was the terminal event. However, sinus arrest is most commonly associated with variable deceleration.[2] From the information presented, it is difficult to know, with certainty, just when this fetus died, as the authors report that a "fresh" stillborn infant was delivered five and a half hours after monitoring was apparently terminated following a 10 minute section of uninterpretable data and lack of fetal heart tones by Doppler (Fig. 2D).

In summary, my impressions are as follows:

1. Late decelerations and a fixed base-line heart rate are present on the tracings submitted by the authors.
2. The instrumentation display of the fetal monitor used by the authors was inadequate to fully interpret the data inasmuch as the combination of a slow paper speed (1 cm. per minute) with a vertical scaling of FHR = 20 beats per centimeter gives the impression of more beat-to-beat variability than would be recorded at 3 cm. per minute with a vertical scaling of FHR = 30 beats per centimeter.
3. There may have been a failure of the monitor or leg plate attachment which could explain the "noisy" uninterpretable segment.
4. There may have been a terminal beat-to-beat arrhythmia (doubtful). Arrhythmia superimposed on an anoxic, acidotic fetus (as suggested by late deceleration, decreased beat-to-beat variability, and fixed base-line heart rate in the tracings in Figs. 2A to 2C) could possibly cause sudden fetal death.
5. It is not clear, from the data presented, just when the fetus died.

I personally believe that the current group of commercially available second-generation FMS's which allow for an option to choose a 1 cm. per minute paper speed, ostensibly to save paper, have inadvertently created a problem. A paper speed of 1 cm. per minute simply does not permit the degree of evaluation of data possible with a 3 cm. per minute paper speed.

I would be interested in the impressions of other readers.

Michael S. Kreitzer, M.D.

Director
Perinatal Intensive Care
St. Peter's Medical Center
254 Easton Avenue
New Brunswick, New Jersey 08903

REFERENCES

1. Paul, R. H.: Obstet. Gynecol. Survey **28:** 453, 1973.
2. Hon, E. H.: An Atlas of Fetal Heart Rate Patterns, 1968, p. 200.

Reply to Ms. Gonzales and Dr. Strahl

To the Editors:

The responses to my letter on sterilization guidelines (AM. J. OBSTET. GYNECOL. 124: 215, 1976) by the Association for Voluntary Sterilization (A.V.S.) represented by Ms. Betty Gonzales (AM. J. OBSTET. GYNECOL. 125: 875, 1976) and by Dr. Margaret Strahl (AM. J. OBSTET. GYNECOL. 125: 1156, 1976), a member of the Board of Directors of A.V.S., and closely associated with Ms. Gonzales in the Division of Information and Education, were unfortunately not accompanied by simultaneous rebuttal. I regret the loss of that opportunity but welcome this occasion to continue our dialogue, even though after the fact.

Ms. Gonzales' opening in "agreement" with my letter is gratuitous, since she is agreeing with the reverse of my position. Sterilization guidelines are necessary to ensure informed consent and prevent coercion or manipulation regarding this permanent irreversible procedure. The right to give *knowing* consent, in possession of *all* relevant information, is as critical a civil right as is the right to terminate fertility or pregnancy. Control of one's own body includes the right to have children as well as the right to forego having children. To equate protecting these rights with male chauvinism or infringement of civil liberty is a distortion.

The official A.V.S. response champions "the right to self-determination . . . for fulfillment of both personal and societal goals." Precisely whose societal goals is A.V.S. referring to? Under conditions of extreme economic deprivation and powerlessness, what degree of reproductive freedom and self-determination does A.V.S. view as possible?

Ms. Gonzales cautions the doctor ". . . not to make moral judgments nor to intrude his personal prejudices," a fascinating reminder from A.V.S. which is heavily funded to promote sterilization programs throughout the world. Incidentally, what "judgments (and) . . . prejudices" is she referring to?

Also, "To pursue [Ms. Gonzales' *reductio ad absurdum*

of] Dr. Rakow's reasoning one step further, one might logically conclude that women . . ." at the time of their death ". . . are in danger of losing their self-esteem because they . . ." no longer have any functional options. Is the naturally occurring, inevitable functional cessation of menopause really seen by A.V.S. as analogous to the surgical termination of fertility at any age?

Which "doctors who are opposed to permanent methods of contraception" is Ms. Gonzales referring to? Those of us who as physicians strongly believe that surgical sterilization (as well as free and legal abortion) should certainly be available in any comprehensive family planning service, in the context of comprehensive medical and social services generally, find this recurrent confusion tiresome. To confuse our position with opposition to sterilization *generally,* or with any Right-to-Life position whatever, is another distortion.

Dr. Strahl reminds us that ". . . tubal ligation has proved far more reliable than *any* temporary . . ." method. If she is referring to pregnancy failure rate, then oral contraceptive agents as well as Depo-Provera* are documented as more "reliable" than most large published sterilization samples. At any rate, our obligation is to provide the patient with *full* information on risks and benefits, as well as available reversible alternatives with the relative risks and benefits of those. Then she can decide the method of *her* choice. That is what we mean by *informed* consent.

In response to my emphasizing the psychological axiom that intact anatomic structure and function are important components of self-image and ego identity, Dr. Strahl makes the interesting point that this is perhaps true regarding the external genitals of men but that regarding the internal genitals of women "it is quite unlikely she ruminates over a loss of procreative potential." This is particularly interesting since *all* other organ structures and functions are internal in both genders. Perhaps gross impairment of cardiac or renal function will not affect body image because those organs "[do] not announce [their] state of being every time [we] walk, sit, . . . and so forth." But, of course, Dr. Strahl intends to separate generative function from all other functions since it is the only *optional* or *potential* function and, therefore, is considered more expendable. However, this distinction does not affect our primary point regarding body image, self-image, or ego identity.

Both respondents emphasized the severe liability of unwanted pregnancy, which ". . . would mutilate their chances for healthy life adaptation and which could indeed foment self-hatred," and which could make "her 'ego identity' comparable to her view of a lowly breeding cow" (Dr. Strahl) or which could be "financially and emotionally devastating" (Ms. Gonzales). I certainly agree in the understanding that unwanted pregnancy is a severe liability and that avoiding such events is a completely valid human motivation. However, sterilization should not be equated with contraception.

Both respondents opposed using psychological standards such as "self-hatred, self-contempt, rejection of gender, and self-mutilating motivation" in evaluating candidates for sterilization. This was one of three clinical situations which I believed warranted *deferring* sterilization. Both respondents misrepresented this point as being *equated* with requests for sterilization, as though employing such standards was ". . . to characterize people seeking fertility termination. . . ." I particularly take issue with A.V.S. and Ms. Gonzales in referring to such clinical criteria as ". . . to arbitrarily impose one's own values on others and to display a prejudice toward childbearing and against women."

Any clinical evaluation of any elective surgical request at any given time has at least some likelihood of yielding a clinical judgment or decision which may or may not comply with patient request. Is this what Ms. Gonzales calls "arbitrary"? If so, then all clinical decisions are indeed arbitrary. Or does Ms. Gonzales perhaps exclude only psychological criteria from the evaluation of this procedure which has exclusively economic and psychosocial motivations?

There is certainly ambiguity on this point. I have interviewed many young women who came to feel so desperate and frustrated by their poverty that they opted for sterilization as their solution, clearly dictated by their economic circumstances. Their view of themselves was primarily hopeless and helpless, self-esteem devastated, self-image shapeless, most clearly communicated by one applicant saying, "A woman is supposed to be a vegetable, so I guess I'll keep being a vegetable." Her decision to be sterilized was clearly viewed as in the direction of her "vegetable" status. The ambiguity of this situation needs wide discussion by the medical profession and by society at large.

I believe that when the individual woman elects sterilization, with full knowledge of risks, alternatives, and later regret factors, and has a cooling period for thinking it over, then her request cannot be denied. Her decision for sterilization, even where predicated on economic and social horror or on self-hatred and self-contempt, then becomes the exercise of an individual right. This position does not diminish the ambiguity.

Incidentally, this dialogue has thus far been joined only by two representatives of the A.V.S. Input from obstetrician-gynecologists stating their positions on this controversial issue would be most welcome.

Raymond W. Rakow, M.D.
Director, Liaison Psychiatry and Consultations
Metropolitan Hospital Center
1901 First Avenue, Rm. 9M29
New York, New York 10029

*The Upjohn Co., 7171 Portage Rd., Kalamazoo, Michigan 49001.

BOOKS

Books received

Cancer Genetics. Edited by Henry T. Lynch. 639 pages, illustrated. Springfield, Illinois, 1976, Charles C Thomas, Publisher. (Price not available.)

Comparative Placentation: Essays in Structure and Function. Edited by D. H. Steven (Monographs for Students of Medicine, Series Editors: R. J. Harrison and A. W. Asscher). 315 pages, illustrated. London, 1976, Academic Press, Inc., Ltd. $12.00 soft cover.

Current Practice in Obstetric and Gynecologic Nursing. Vol. I. Edited by Leota Kester McNall and Janet Trask Galeener. 254 pages, illustrated. St. Louis, 1976, The C. V. Mosby Company. $10.50 hard cover. $7.50 soft cover.

Current Practice in Pediatric Nursing. Vol. I. Edited by Patricia A. Brandt, Peggy L. Chinn, and Mary Ellen Smith. 241 pages. St. Louis, 1976, The C. V. Mosby Company. $10.50 hard cover. $7.50 soft cover.

Malnutrition and Brain Development. Myron Winick. 169 pages, illustrated. New York, 1976, Oxford University Press. $9.95.

Medical Nemesis: The Expropriation of Health. Ivan Illich. 294 pages. New York, 1976, Pantheon Books. $8.95.

Perinatal Pharmacology and Therapeutics. Edited by Bernard L. Mirkin. 455 pages, illustrated. New York, 1976, Academic Press, Inc. (Price not available.)

Physiological Effects of Immunity Against Reproductive Hormones. Clinical and Experimental Immunoreproduction 3. Edited by R. G. Edwards and M. H. Johnson. 283 pages, illustrated. New York, 1976, Cambridge University Press. $19.95.

Regulation of Human Fertility. Edited by Kamran S. Moghissi and Tommy N. Evans. 318 pages, illustrated. Detroit, 1976, Wayne State University Press. $22.00 soft cover.

Teaching of Chronic Illness and Aging. Vol. 2. Edited by Duncan W. Clark and T. Franklin Williams. John E. Fogarty International Center Series on the Teaching of Preventive Medicine. 132 pages. Bethesda, Maryland, 1975, National Institutes of Health. (Department of Health, Education, and Welfare Publication No. [NIH] 75-876.) $5.85.

INDEX TO ADVERTISERS

Abbott Laboratories
Fero-Folic-500/Iberet-Folic-500 ——— 16, 17
Ogen ——— 50, 51, 52

Ayerst Laboratories
Premarin ——— 45, 46, 47, 48

B-D Electrodyne
Fetal Monitors ——— 40, 41

Carnrick Laboratories
Hormonin ——— 6

Corometrics Medical Systems, Inc.
Fetal Monitors ——— 29

Flint Laboratories
Synthroid ——— 22, 23, 24

Frigitronics of Connecticut Inc.
Frigi Colposcope ——— 44

Hamot Medical Center
Classified ——— 10

Holland-Rantos Co., Inc.
Koromex ——— 53

Mead Johnson Laboratories
Estrace ——— 30, 31, 32
Peri-Colace ——— Fourth Cover

Merrell-National Laboratories
AVC ——— 12

Ortho Pharmaceutical Corporation
ModiCon ——— 56, 57, 5
Monistat ———
Ortho-Novum 1/80 ——— 37, 3
Sultrin ——— 42, 4

Purdue Frederick Company, The
Senokot S ——— 1

Roche Laboratories
Azo Gantanol ——— 18, 1

Searle & Co., G.D.
Cu-7 ——— Second Cover,

Sonicaid, Inc.
Fetal Heart Detectors ——— 1

Storz Endoscopy, Karl-America, Inc.
Laparoscopes ——— 2,

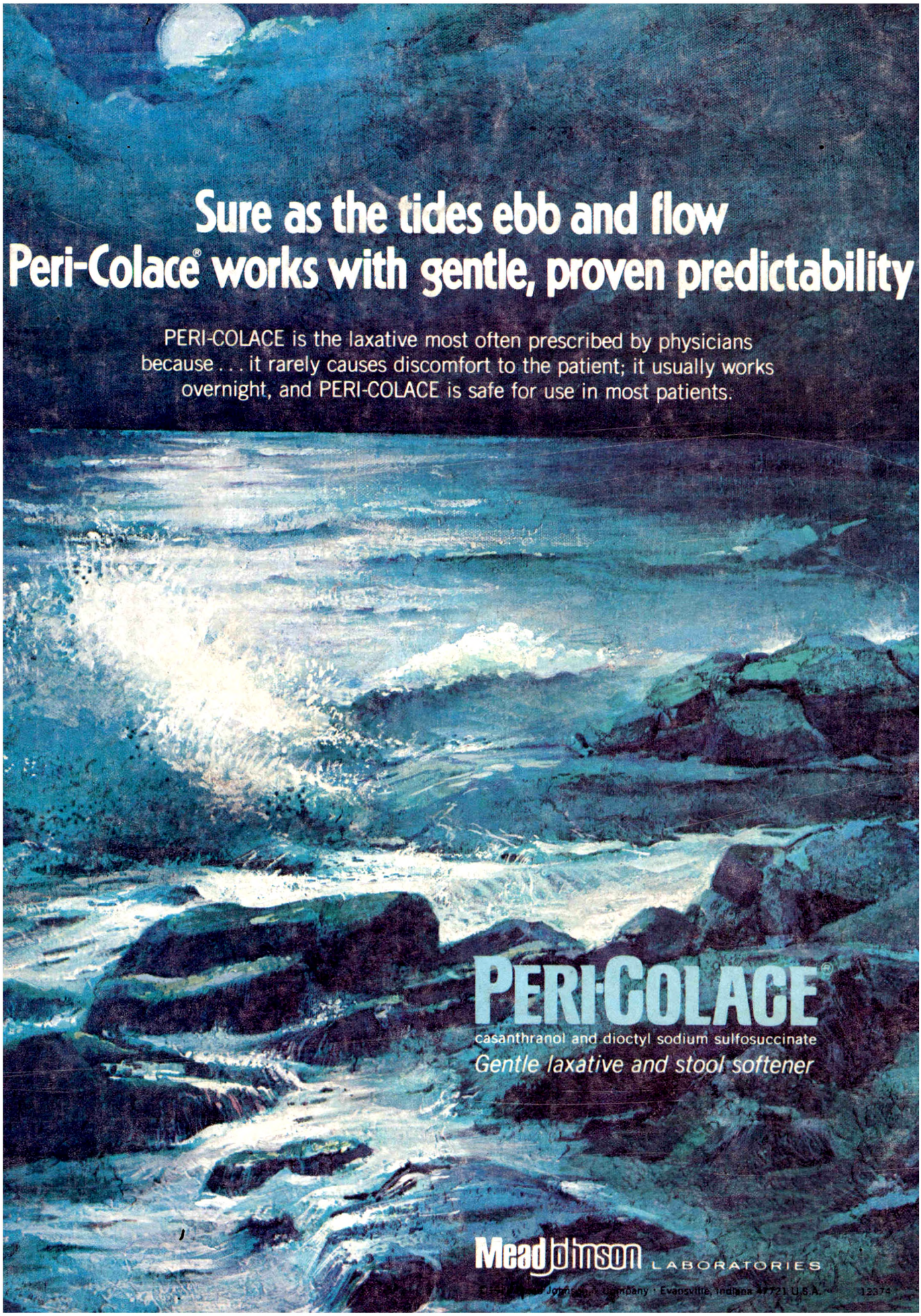
University of Southern California
Postgraduate Course ——— 2

Warner/Chilcott
Vakutage ——— 33, 34, 35, 3

Welch Allyn, Inc.
Disposable Vaginal Specula ———

Wyeth Laboratories
Lo/Ovral ——— 26, 27, 2
Ovral ——— 4

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.


Sure as the tides ebb and flow
Peri-Colace® works with gentle, proven predictability
PERI-COLACE is the laxative most often prescribed by physicians because . . . it rarely causes discomfort to the patient; it usually works overnight, and PERI-COLACE is safe for use in most patients.
PERI-COLACE®
casanthranol and dioctyl sodium sulfosuccinate
Gentle laxative and stool softener
Mead Johnson LABORATORIES
Mead Johnson & Company • Evansville, Indiana 47721 U.S.A.
12374

Rec.
19.2.77

October 1, 1976
volume 126, *number* 3

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

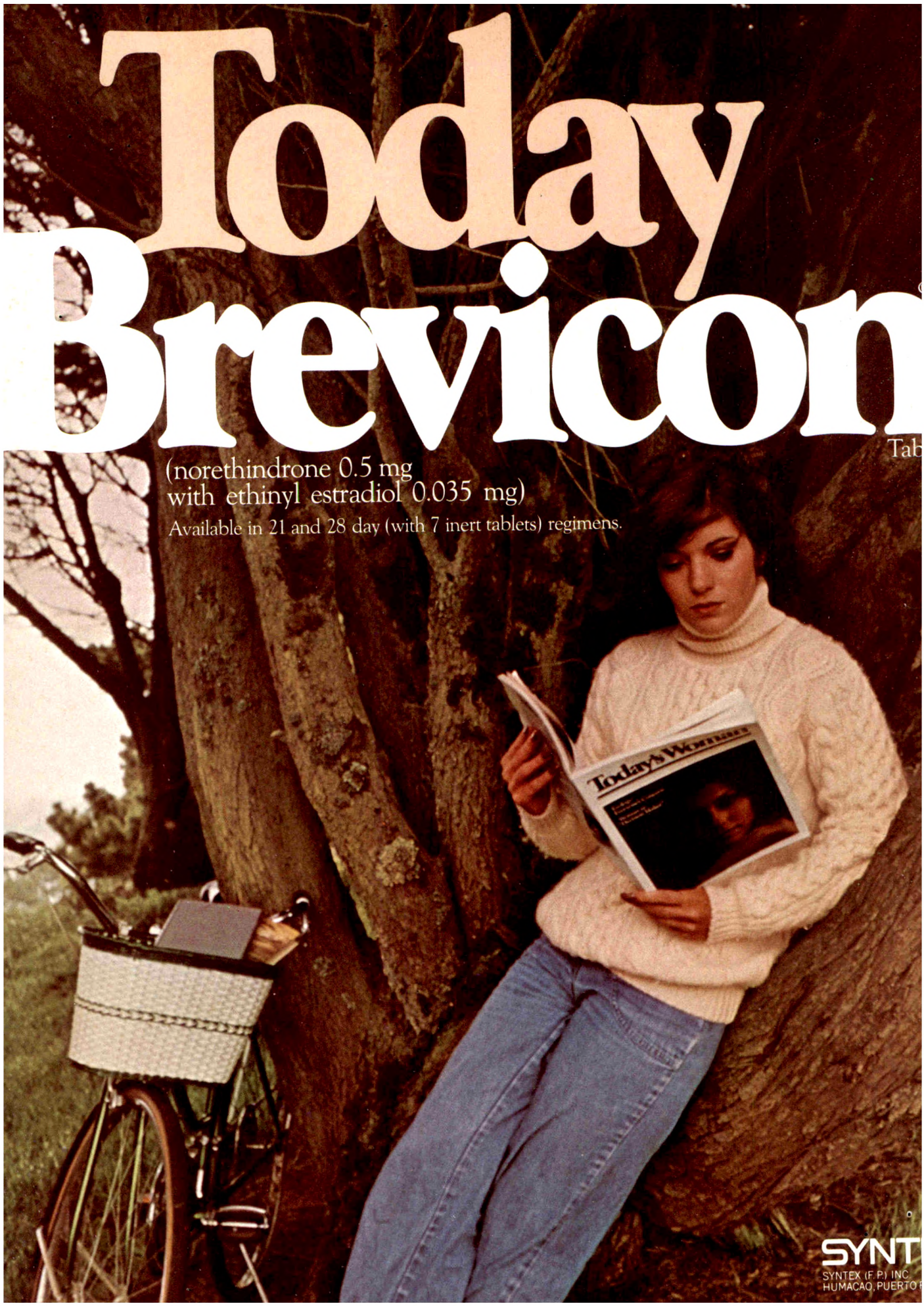
Official Publication

AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

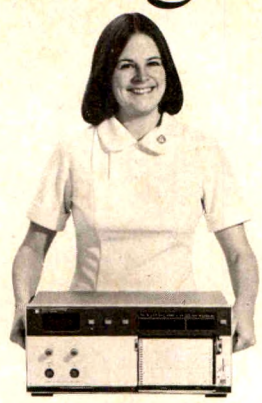
Published by

THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (3) 301-410 (1976)


Today
Brevicon
Tab
(norethindrone 0.5 mg
with ethinyl estradiol 0.035 mg)
Available in 21 and 28 day (with 7 inert tablets) regimens.
Today's Woman
SYNT
SYNTEX (F.P.) INC.
HUMACAO, PUERTO

a significant contribution to fetal monitoring:



SIMPLICITY

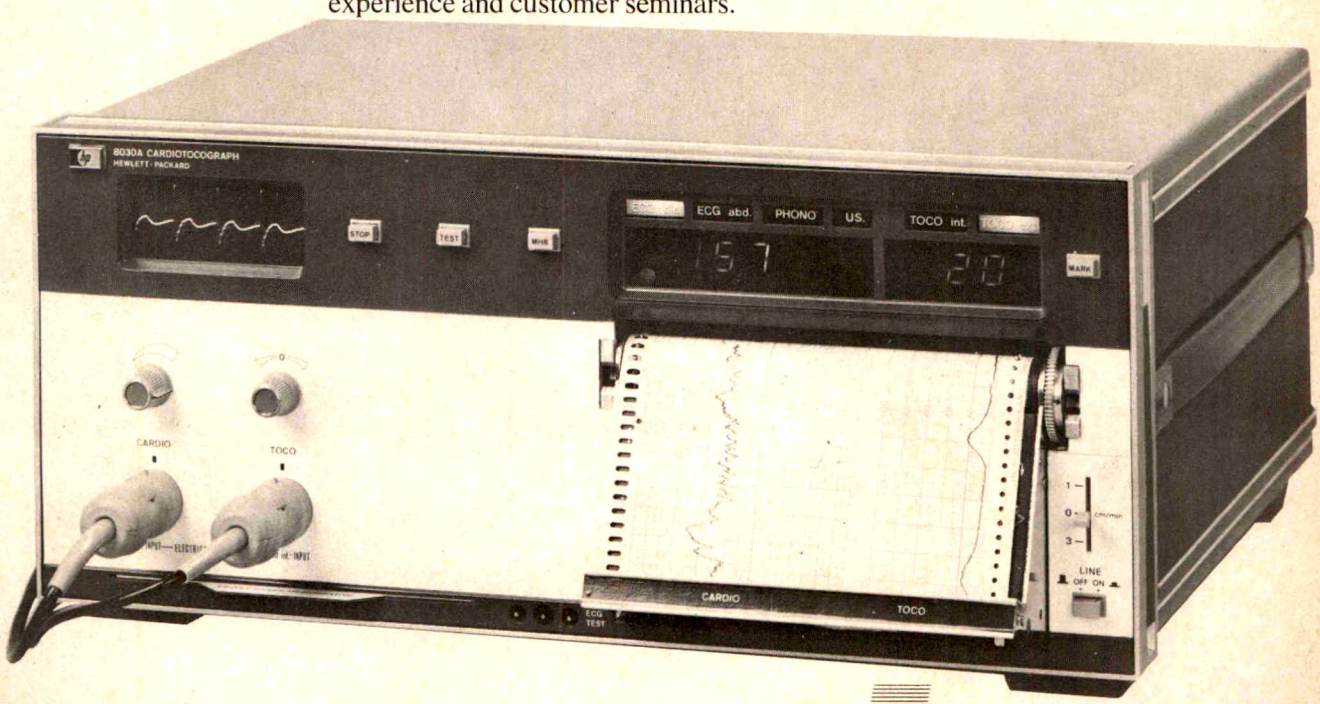
HP's new 8030A Cardiotocograph is a major technological contribution to fetal/maternal care for a very simple reason: it greatly simplifies the whole process of consistently getting good, clear, clinical data on fetal response to labor. It allows you to give your major attention to your *patients*—not to the electronics.

How? By *automating* many of the Cardiotocograph's operations...providing clear, rapid *checks* on data quality...*minimizing* monitoring preparation and instrument set-up time.

For example: simply by plugging in a Fetal Heart Rate transducer, the 8030 selects the operating mode, announces the mode by lighted indicator, calibrates the input signal and adjusts the sensitivity—automatically. And for quick determination of the best position for the FHR transducer, a built-in, non-fade scope gives a bright trace display (which you can "freeze" by pressing a STOP button, for detailed examination). Further, pressing the TEST pushbutton checks instrument logic, digital display and recorder, and with the FHR transducer connected, the scope as well.

All information can be seen at a glance: FHR and labor on large digital displays... FHR and labor recording methods in use, on lighted status indicators...each valid FHR measurement by acceptance lamp flash...poor electrode contact, detached electrodes or transducer by INOP lamp.

To have exactly the monitoring capabilities *you* require, the state-of-the-art 8030A can be ordered with ultrasound, direct FECG and external labor inputs—or with abdominal FECG, heart sound and/or intrauterine pressure inputs added, at time of purchase or later. Call or write your nearby HP field office for complete details of this modern, easy-to-use fetal monitoring system, fully backed by HP service, experience and customer seminars.



HEWLETT hp PACKARD

Sales and service from 172 offices in 65 countries.

17601

Two reasons your atrophic vaginitis patient will really appreciate ORTHO Dienestrol Cream:

TRADEMARK

(dienestrol 0.01%)

1 Rapid relief of her symptoms – itching, burning, dyspareunia, discharge



© Ortho Pharmaceutical Corporation

2 Provides economical relief of her symptoms that's easy on her pocketbook...an important consideration if she's on long-term maintenance therapy or a fixed income



Indications: Dienestrol Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases. *Contraindications:* Malignancies or precarcinomatous lesions of the vagina or vulva. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy. *Warning:* Vaginal adenosis has been reported in 30% to 90% of postpubertal girls and young women whose mothers received diethylstilbestrol or a closely related congener during pregnancy. This condition was found most frequently in those cases where DES had been given in early pregnancy (first 12 weeks). The significance of this finding with respect to potential for development of vaginal adenocarcinoma is unknown. Periodic examination of such patients is recommended. *Precautions:* In pruritus vulvae due to infectious conditions, the organism responsible for the infection should be treated with a specific agent. *Dosage:* One or two applicatorsful per day for one or two weeks, then gradually reduced to one-half initial dosage for a similar period. A maintenance dosage of one applicatorful, one to three times a week may be used after restoration of the vaginal mucosa has been achieved. *Supplied:* Available in 2.75 oz. (78 g) tubes with or without ORTHO* Measured-Dose Applicator.

*TRADEMARK

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

No. 3
As potent as the pain it relieves.

e.g. postpartum pain



NOT TOO LITTLE
- as potent as the pain you need to relieve in patients with fractures, sprains, strains, wounds, contusions, and the pain of surgical convalescence
- unlike acetaminophen/codeine combinations, it does not sacrifice anti-inflammatory action

NOT TOO MUCH
- potent—yet not excessive
- addiction liability low

NOT TOO EXPENSIVE
- brand-name quality, yet reasonable in cost
- readily available in both hospital and local pharmacies

CIII CONVENIENCE
- telephone Rx in most states, up to 5 refills in 6 months at your discretion (where state law permits)

EMPIRIN® COMPOUND WITH CODEINE, NO. 3

codeine phosphate* (32.4 mg) gr ½
Each tablet also contains: aspirin gr 3½, phenacetin gr 2½, caffeine gr ½. *Warning—may be habit-forming.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

October 1

1976

Clinical opinion

Cigarette smoking, use of oral contraceptives, and myocardial infarction 301

Anrudh K. Jain, Ph.D.

New York, New York

Obstetrics

The effect of active immunity against placental proteins on pregnancy in monkeys 308

John P. Gusdon, Jr., M.D., with the technical assistance of Candace C. Witherow

Winston-Salem, North Carolina

Human uterine artery responses to lidocaine 313

Charles P. Gibbs, M.D., and Stephen C. Noel, Ph.D.

Gainesville, Florida

(Contents continued on page 7)

Vol. 126, No. 3, October 1, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.

Colposcope 9—has ZEISS Quality at Low Price

This corrects the misconception:

that Zeiss Colposcopes are too expensive for use in private practice.

Definitely not Colposcope 9 with its easy fine-focusing device. It was designed, and priced, specifically for use in the office examining room—so that gynecologists can have the same optical excellence and engineering precision in their offices that the clinic demands.

With Colposcope 9, office colposcopy is as affordable as it is necessary for DES detection. And it is advisable in routine examinations, especially in evaluating patients with class 2 pap smears; it helps physicians to better understand early cervical neoplasia, and reduces dramatically the inherent false-negative rate of vaginal sampling.

Three stands—the wall mount that keeps the floor uncluttered; the floor stand, easily movable from room to room; and the convenient mount for the examining table.

Adding accessories is a snap—you can do it in your office.

In contrast to other instruments, there's no need to return Colposcope 9 to have accessories installed.

You'll find the photographic accessories particularly valuable for patient documentation before and after treatment, especially when legal aspects are involved.

Write or call for details or a demonstration.

Nationwide service.

Carl Zeiss, Inc., 444 5th Avenue, New York, N.Y. 10018 (212) 730-4400. Branches in: Atlanta, Boston, Chicago, Columbus, Houston, Los Angeles, San Francisco, Washington, D.C. In Canada: 45 Valleybrook Drive, Don Mills, Ont., M3B 2S6. Or call (416) 449-4660.



ZEISS

THE GREAT NAME IN OPTICS

CARL ZEISS WEST GERMANY

Many accessories available:

1. A three-step magnification changer for both viewer and photographic attachments simultaneously.

2. A Polaroid® camera with increased flash power supply for better illumination.

3. A full-frame 35mm camera.

4. The new Zeiss-Urban 35mm split-frame stereo photo adapter for color stereophotographs on one frame in a single exposure.

5. A co-observation tube for viewing the field exactly as the examining physician views it — in both white and red-free light.

Contents continued from page 5

Repeat aborters 316

Sandra M. Schneider and Douglass S. Thompson
Pittsburgh, Pennsylvania

Fetal immune response following prematurely ruptured membranes 321

Lars L. Cederqvist, M.D., Linda C. Francis, B.S., Ioannis A. Zervoudakis, M.D., Carl G. Becker, M.D., and Stephen D. Litwin, M.D.
New York, New York

Intra-amniotic urea and prostaglandin $F_{2\alpha}$ for midtrimester abortion: A modified regimen 328

Ronald T. Burkman, M.D., Milagros F. Atienza, M.D., Theodore M. King, M.D., Ph.D., and Lonnie S. Burnett, M.D.
Baltimore, Maryland

Spontaneous rupture of the liver in pregnancy: A report of eight cases 334

Lester T. Hibbard, M.D.
Los Angeles, California

Abnormality in metabolism of ^{15}N-labeled nitrate in toxemia 339

D. S. McLaren, A. Mroueh, and W. W. C. Read
Beirut, Lebanon

Fetus, placenta, and newborn

Effect of ritodrine infusion on uterine and umbilical blood flow in pregnant sheep 343

Richard A. Ehrenkranz, M.D., Adrian M. Walker, Ph.D., Gary K. Oakes, M.D., Margaret K. McLaughlin, M.S., and Ronald A. Chez, M.D.
Bethesda, Maryland

Placental cultures for cytogenetic assessment in saline-aborted fetuses 350

H. Allen Gardner, M.D., M.Sc., F.R.C.P.(C.), E. Martha Wood, B.A., R.T., and Ellyn Stecker, B.A.
Toronto, Ontario, Canada

Umbilical cord compression associated with amniotomy: Laboratory observations 353

Steven G. Gabbe, M.D., Bruce B. Ettinger, M.D., Roger K. Freeman, M.D., and Chester B. Martin, M.D.
Los Angeles, California

Incorporation of ^{14}C-1-palmitate into rabbit fetal lipids in vivo 356

J. J. Biezenski, M.D.
Chicago, Illinois

(Contents continued on page 9)

The causes of vaginitis are multiple



You can depend on AVC... therapy that combats major vaginal pathogens and provides rapid symptomatic relief.*

***Indications:** Based on a review of AVC by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually *Trichomonas vaginalis, Candida albicans,* or *Hemophilus vaginalis)* is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Known sensitivity to sulfonamides.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.

Dosage: 1 applicatorful (about 6 g.) or 1 suppository intravaginally once or twice daily.

Supplied: Cream–4 ounce tube with applicator. Suppositories–Box of 16 with inserter.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

4-6744 (6049)

The treatment is singular.

AVC™

Cream (aminacrine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%)

Suppositories (aminacrine hydrochloride 0.014 g., sulfanilamide 1.05 g., allantoin 0.14 g.)

Contents continued from page 7

Gynecology

The effect of vaginal lubricants on *Neisseria gonorrhoeae* 365
Balwant Singh, Ph.D., and John C. Cutler, M.D.
Pittsburgh, Pennsylvania

Cellular hypersensitivity in patients with adenomatous hyperplasia and adenocarcinoma of the endometrium 370
Sidney Y. Chen, M.D., Carmel J. Cohen, M.D., and David Koffler, M.D.
New York, New York

Fallopian tube and ovarian hydrocarbons 374
Eric J. Singh, Ph.D., Frederick P. Zuspan, M.D., Iracema M. Baccarini, M.D., and Atef Moawad, M.D.
Chicago, Illinois

Progestational activity of Danazol in the human female subject 378
Anne Colston Wentz, M.D., Georgeanna Seegar Jones, M.D., Karan, C. Sapp, and Theodore M. King, M.D., Ph.D.
Baltimore, Maryland

The effect of prophylactic ampicillin on pelvic infection following vaginal hysterectomy 385
M. W. Glover, M.D., and J. R. van Nagell, Jr., M.D.
Lexington, Kentucky

Classic pages

Classic pages 389

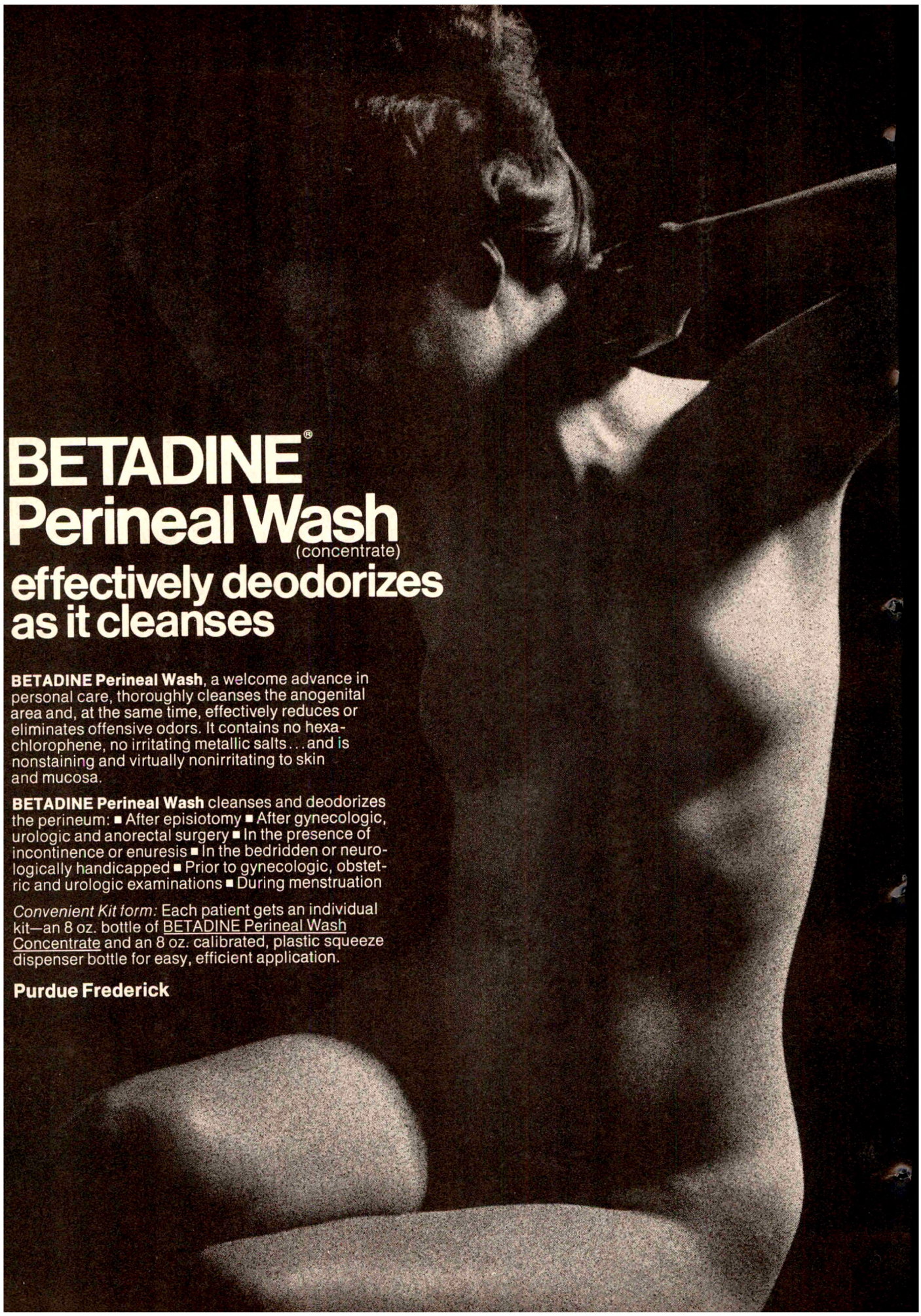
Current developments

Mercury toxicity in the pregnant woman, fetus, and newborn infant 390
Brian J. Koos, M.D., and Lawrence D. Longo, M.D.
Loma Linda, California

Items

Items 410

(Information for authors on page 19)



BETADINE® Perineal Wash (concentrate) effectively deodorizes as it cleanses

BETADINE Perineal Wash, a welcome advance in personal care, thoroughly cleanses the anogenital area and, at the same time, effectively reduces or eliminates offensive odors. It contains no hexachlorophene, no irritating metallic salts...and is nonstaining and virtually nonirritating to skin and mucosa.

BETADINE Perineal Wash cleanses and deodorizes the perineum: ■ After episiotomy ■ After gynecologic, urologic and anorectal surgery ■ In the presence of incontinence or enuresis ■ In the bedridden or neurologically handicapped ■ Prior to gynecologic, obstetric and urologic examinations ■ During menstruation

Convenient Kit form: Each patient gets an individual kit—an 8 oz. bottle of BETADINE Perineal Wash Concentrate and an 8 oz. calibrated, plastic squeeze dispenser bottle for easy, efficient application.

Purdue Frederick

Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

Advisory committee on policy

David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*





"See you in another six months..."

...for a routine checkup, not an oral contraceptive problem.

And that's been the experience of thousands of women—over hundreds of thousands of cycles—with Norlestrin.

The sort of experience that emphasizes the efficacy and acceptance of Norlestrin.

Norlestrin

- the first oral contraceptive marketed with 50 mcg estrogen
- two ratios to choose from—either 2.5 or 1 mg progestin—both effective and both combined with 50 mcg of estrogen
- a low incidence of annoying side effects which some patients find unacceptable with other dosages or products*
- a regimen with few problems—28-day non-stop—particularly well-suited for busy patients who have difficulty keeping track of the days

this year or any year

Norlestrin® Fe 2.5mg

Each pink tablet contains 2.5 mg norethindrone acetate, 50 mcg ethinyl estradiol. Each brown tablet contains 75 mg ferrous fumarate, USP.

Norlestrin Fe 1mg

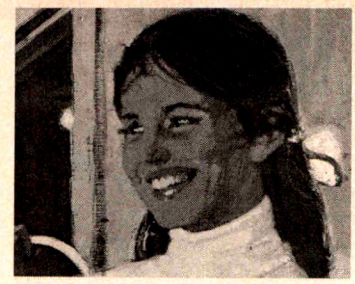
Each yellow tablet contains 1 mg norethindrone acetate, 50 mcg ethinyl estradiol. Each brown tablet contains 75 mg ferrous fumarate, USP.

*Both serious and minor adverse reactions have been reported by women taking oral contraceptives. The physician should be alert to their manifestations and should carefully review the following page for prescribing information.

PARKE-DAVIS

Norlestrin

(norethindrone acetate and ethinyl estradiol tablets, NF)



BRIEF SUMMARY OF PRESCRIBING INFORMATION

ACTIONS

Norlestrin achieves its contraceptive effect primarily by inhibition of ovulation through gonadotropin suppression. It is possible that other sites of action such as changes in cervical mucus and in the endometrium may contribute to the high efficacy of oral contraceptives.

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

Norlestrin is indicated for the control of conception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
3. Since the safety of Norlestrin (norethindrone acetate and ethinyl estradiol) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.
4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.
2. Endocrine and possibly liver function tests may be affected by treatment with Norlestrin. Therefore, if such tests are abnormal in a patient taking Norlestrin, it is recommended that they be repeated after the drug has been withdrawn for two months.
3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size.
4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.
6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
7. Any possible influence of prolonged Norlestrin therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.
8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Norlestrin therapy.
9. The age of the patient constitutes no absolute limiting factor, although treatment with Norlestrin may mask the onset of the climacteric.
10. The pathologist should be advised of Norlestrin therapy when relevant specimens are submitted.
11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Pulmonary embolism
Cerebral thrombosis

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea during and after treatment
Edema
Chloasma or melasma
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)
Changes in cervical erosion and cervical secretions
Suppression of lactation when given immediately postpartum
Cholestatic jaundice
Migraine
Rash (allergic)
Rise in blood pressure in susceptible individuals
Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post-treatment
Premenstrual-like syndrome
Changes in libido
Changes in appetite
Cystitis-like syndrome
Headache
Nervousness
Dizziness
Fatigue
Backache
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: increased sulfobromophthalein retention and other tests; Coagulation tests: increase in prothrombin Factors VII, VIII, IX, and X; Thyroid function: increase in PBI, and butanol-extractable protein-bound iodine and decrease in T^3 uptake values; Metyrapone test; Pregnanediol determination.

SPECIAL NOTE

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new compact on the fifth day (Day 5). Persistent bleeding which is not controlled by this method indicates the need for re-examination of the patient, at which time nonfunctional causes should be borne in mind.

SD

1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. *J Coll Gen Pract*, **13:**267-279, 1967.
2. Inman, W H W and Vessey M P : Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. *Br Med J*, **2:**193-199, 1968.
3. Vessey M P and Doll R : Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. *Br Med J* **2:**651-657, 1969.
4. Sartwell P E, Masi A T, Arthes F G, Greene G R and Smith H E : Thromboembolism and Oral Contraceptives: An Epidemiological Case–Control Study. *Am J Epidemiol* **90:**365-380, 1969.

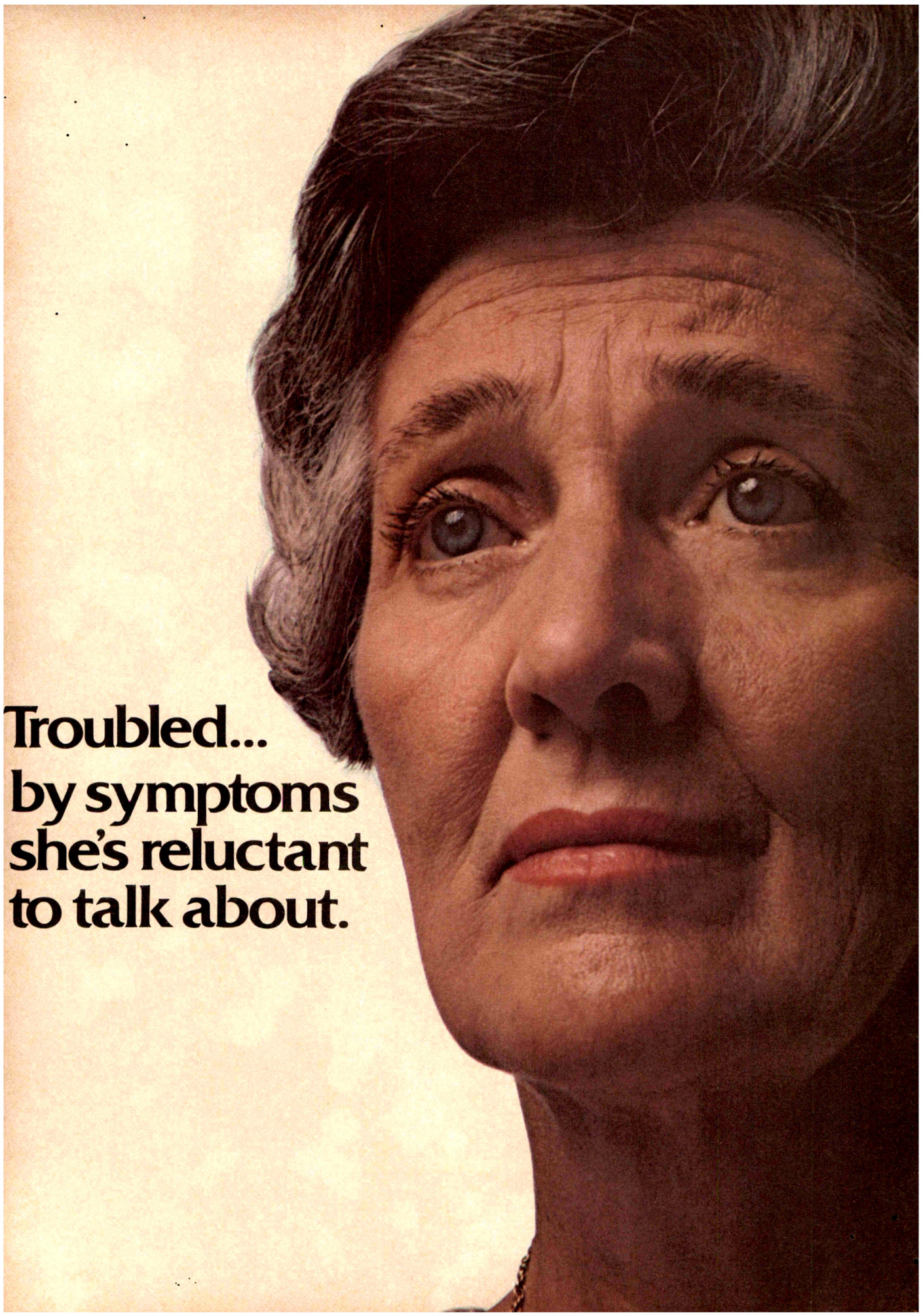
PARKE-DAVIS

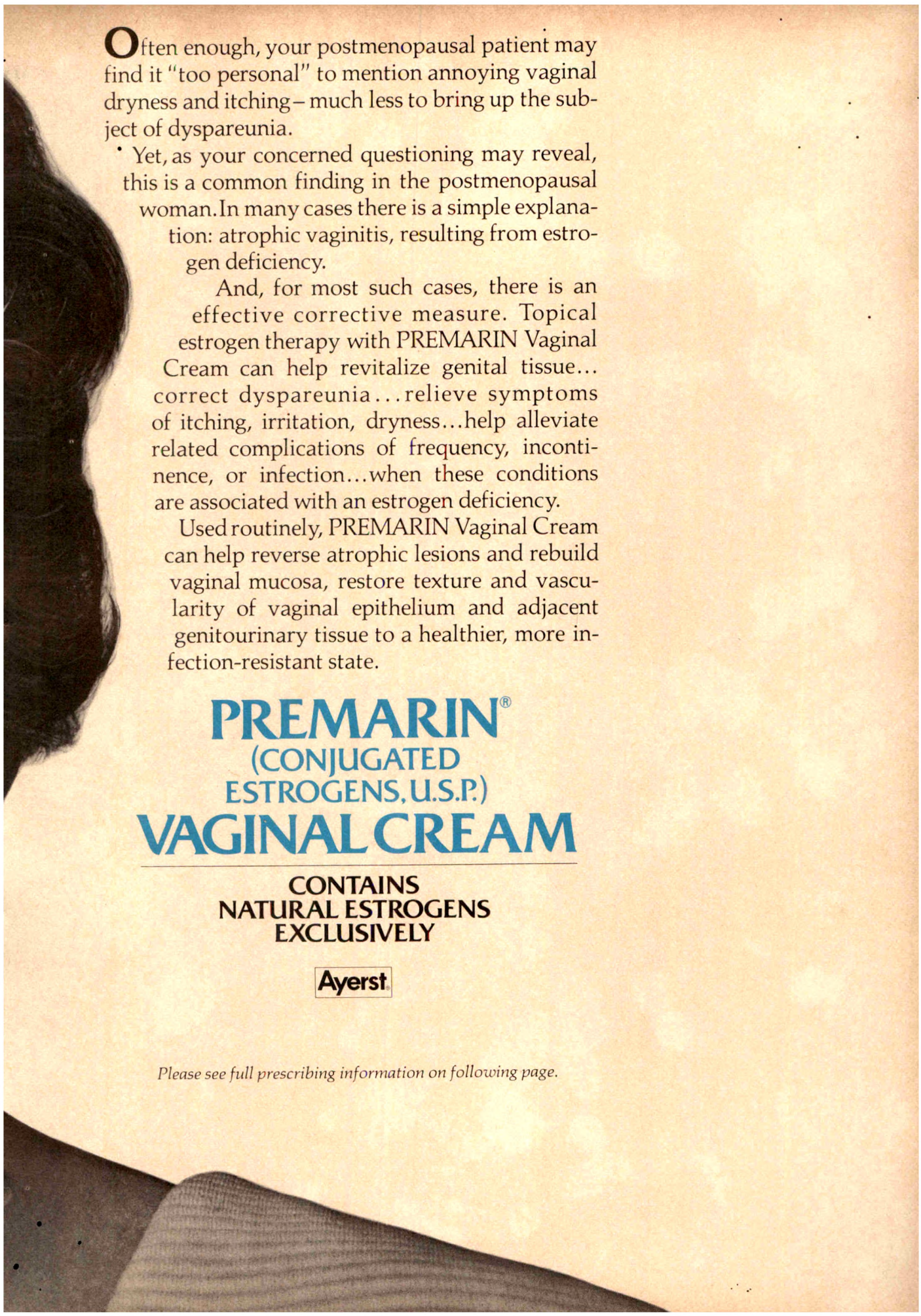
PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY


Troubled...
by symptoms
she's reluctant
to talk about.



Often enough, your postmenopausal patient may find it "too personal" to mention annoying vaginal dryness and itching – much less to bring up the subject of dyspareunia.

Yet, as your concerned questioning may reveal, this is a common finding in the postmenopausal woman. In many cases there is a simple explanation: atrophic vaginitis, resulting from estrogen deficiency.

And, for most such cases, there is an effective corrective measure. Topical estrogen therapy with PREMARIN Vaginal Cream can help revitalize genital tissue... correct dyspareunia...relieve symptoms of itching, irritation, dryness...help alleviate related complications of frequency, incontinence, or infection...when these conditions are associated with an estrogen deficiency.

Used routinely, PREMARIN Vaginal Cream can help reverse atrophic lesions and rebuild vaginal mucosa, restore texture and vascularity of vaginal epithelium and adjacent genitourinary tissue to a healthier, more infection-resistant state.

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.)
VAGINAL CREAM

CONTAINS NATURAL ESTROGENS EXCLUSIVELY

Ayerst

Please see full prescribing information on following page.

(Complete text of package circular.)

PREMARIN® Vaginal Cream
(CONJUGATED ESTROGENS, U.S.P.)
in a nonliquefying base

DESCRIPTION: Each gram contains 0.625 mg Conjugated Estrogens, U.S.P., in a nonliquefying base.

PREMARIN (Conjugated Estrogens, U.S.P.) is a mixture of estrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 α-dihydroequilin, together with smaller amounts of 17 α-estradiol, equilenin, and 17 α-dihydroequilenin as salts of their sulfate esters.

ACTION: PREMARIN Vaginal Cream provides the local estrogenic activity of topical estrogen.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than nonusers to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients.

Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued.

It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

INDICATIONS: PREMARIN Vaginal Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

CONTRAINDICATIONS: PREMARIN Vaginal Cream is contraindicated in: Patients hypersensitive to its ingredients.

Patients with markedly impaired liver function.

Patients with known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible.

Patients with known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium.

Undiagnosed abnormal genital bleeding.

Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or with a past history of these conditions.

WARNINGS: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately.

Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, the effect of estrogen medication should be stopped.

A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

PRECAUTIONS: Diagnostic measures should be taken to eliminate the possibility of neoplasia or gonorrhea.

The use of PREMARIN Vaginal Cream does not preclude the use of appropriate antimicrobial therapy in the presence of trichomonal, monilial, or bacterial infection.

Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.

Because of estrogen-induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution.

Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely.

Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

A pretreatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals.

When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females.

Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months.

Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

ADVERSE REACTIONS: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis; pulmonary embolism; cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following reactions: coronary thrombosis; neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis).

The following adverse reactions are known to occur in patients receiving estrogens: nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting or withdrawal bleeding; breast tenderness and enlargement; change in body weight (increase or decrease); headache; increased cervical mucus; allergic rash; reactivation of endometriosis; aggravation of migraine headaches; hepatic cutaneous porphyria becoming manifest; cholestatic jaundice; rise in blood pressure in susceptible individuals; mental depression; cystitis-like syndrome; loss of scalp hair; erythema nodosum; hemorrhagic eruption; premenstrual-like syndrome; changes in libido; changes in appetite; nervousness; dizziness; fatigue; backache; erythema multiforme; itching; possible diminution in lactation when given immediately postpartum; irritability; malaise.

DOSAGE AND ADMINISTRATION: *Usual dosage:* Intravaginally or topically, 2 to 4 g daily, depending on the severity of the condition. In postmenopausal surgery, therapy is suggested 10 days before and 10 days following intervention.

HOW SUPPLIED: No. 872—PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains spermaceti, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz (42.5 g) tube.

REFERENCES: 1. Royal College of General Practitioners: Oral contraception and thrombo-embolic disease, J. Coll. Gen. Pract. *13*:267, 1967. 2. Inman, W.H.W., and Vessey, M.P.: Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age, Br. Med. J. *2*:193, 1968. 3. Vessey, M.P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report, Br. Med. J. *2*:651, 1969. 4. Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E.: Thromboembolism and oral contraceptives: An epidemiological case-control study, Am. J. Epidemiol. *90*:365 (Nov.) 1969. 5. Inman, W.H.W., Vessey, M.P., Westerholm, B., and Engelund, A.: Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs, Br. Med. J. *2*:203, 1970. 6. Herbst, A.L., Ulfelder, H., and Poskanzer, D.C.: Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women, N. Engl. J. Med. *284*:878 (Apr. 22) 1971.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

7648

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave.,
Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2,* Current Investigation and Clinical Opinion, limited to *6,* and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

On the OB/GYN service

Mixed infection* may not require "mixed therapy"



*due to susceptible strains of indicated organisms

GEOPEN® IM/IV

(DISODIUM CARBENICILLIN)

1-gm, 2-gm, 5-gm, and 10-gm vials

for treatment of infections due to anaerobes* and gram-negative aerobes* with *one* antibiotic

*susceptible strains of indicated organisms

Indications: Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa, Proteus* species (particularly indole-positive strains), and certain *Escherichia coli.* Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Severe systemic infections and septicemia; genitourinary tract infections including those due to *Neisseria gonorrhoeae, Enterobacter,* and *Streptococcus faecalis* (enterococcus); acute and chronic respiratory infections (though clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft-tissue infections. Also indicated in the following infections due to susceptible anaerobic bacteria: Septicemia; lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis; skin and soft-tissue infections.

Although indicated primarily in gram-negative infections, activity against gram-positive organisms should be kept in mind when both gram-positive and gram-negative organisms are isolated (see **Actions**).

In infections due to certain susceptible strains of *Ps. aeruginosa,* clinical efficacy may be enhanced by combined therapy with gentamicin sulfate in full therapeutic dosages (see gentamicin sulfate package insert).

NOTE: During therapy sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms.

Actions: Organisms found to be susceptible *in vitro* include: GRAM-NEGATIVE ORGANISMS—*Ps. aeruginosa, Proteus mirabilis, Pr. morgani, Pr. rettgeri, Pr. vulgaris, E. coli, Enterobacter* spp, *Salmonella* spp, *Hemophilus influenzae, Neisseria* spp, *Bacteroides* spp, and *Fusobacterium* spp.

GRAM-POSITIVE ORGANISMS—*Staphylococcus aureus* (non-penicillinase producing), *Staph. albus, Diplococcus pneumoniae,* beta-hemolytic streptococci, *Str. faecalis, Clostridium* spp, *Peptococcus* spp, and *Peptostreptococcus* spp.

In vitro synergism between Geopen and gentamicin sulfate has been demonstrated for certain strains of *Ps. aeruginosa.*

Some newly emerging pathogenic strains of *Herellea, Mima, Citrobacter,* and *Serratia* have also shown *in vitro* susceptibility.

Not stable in the presence of penicillinase. Most *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly.

Contraindications: Known penicillin allergy.

Warnings: Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations; if bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy.

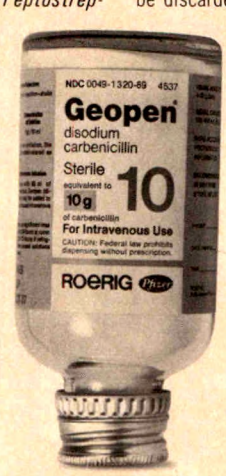
Individuals with history of penicillin hypersensitivity reactions have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of carbenicillin therapy considered, unless the infection is life threatening and only amenable to carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Precautions: As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* spp and *Serratia* spp, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. In a few patients receiving high doses, hypokalemia has been reported; periodic serum potassium determinations should be made and corrective measures should be implemented when necessary. As with any penicillin preparation, an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. Cases of gonorrhea with a suspected primary lesion of syphilis should have darkfield examinations before treatment. In all other cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. Intravenous infusion should be given as slowly as possible. Reconstituted solution should be discarded after 24 hours if stored at room temperature, after 72 hours if refrigerated. The maximum recommended dose is 40 gm per day; intramuscular injections should not exceed 2 gm per injection.



Adverse Reactions: *Hypersensitivity Reactions*—Skin rashes, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*—Nausea. *Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia. *Blood, Hepatic, and Renal Studies*—SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of hepatic or renal disorders have been demonstrated. CNS—Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Other*—Pain at the site of injection, rarely accompanied by induration; in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Vein Irritation and Phlebitis*—Particularly when undiluted solution is injected directly into the vein.

How Supplied: Available in 1-gm, 2-gm, 5-gm, and 10-gm vials.

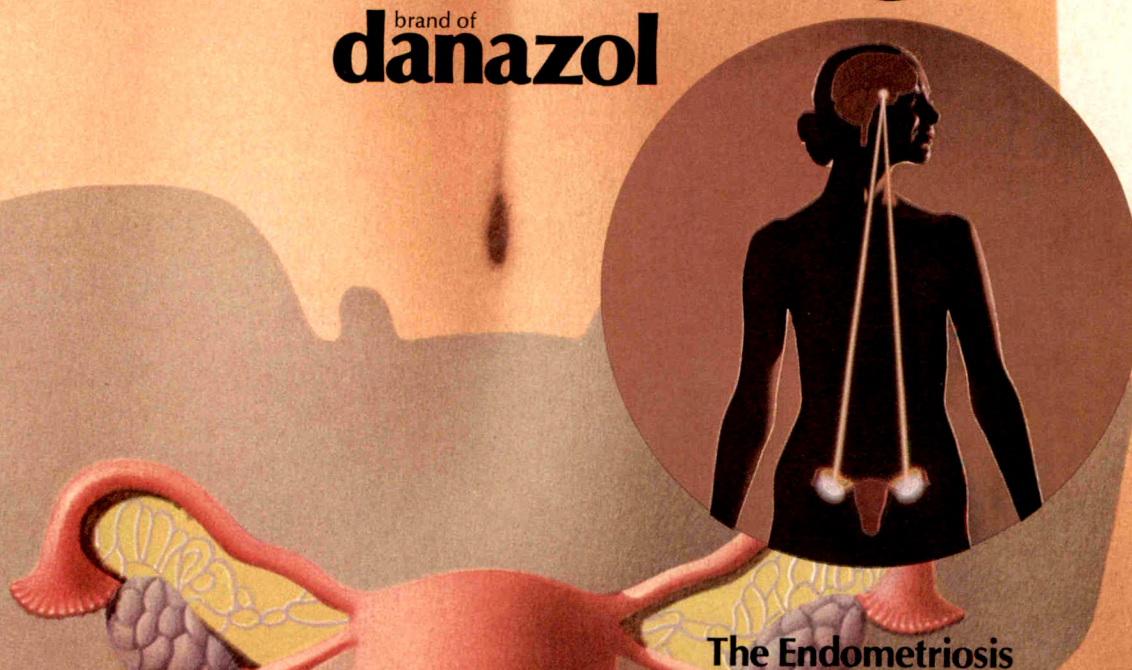
Before prescribing or administering, see package circular or PDR.

ROERIG Pfizer A division of Pfizer Pharmaceuticals New York, New York 10017

Winthrop Laboratories announces a new gonadotropin inhibitor

Danocrine®

brand of
danazol



The Endometriosis Signs and Symptoms Profile

Dysmenorrhea

Pelvic Pain

Dyspareunia

Induration of the cul-de-sac

Infertility

Now—a pharmacologic agent specifically for endometriosis

- proven both effective and well accepted
- in selected cases, an alternative to surgery and to existing hormonal therapy*

After Treatment with Danocrine® In 267 patients†

Complete or partial relief in 96% of 227 patients with this symptom	Endometriosis can be characterized by any of these signs and symptoms. After initiation of therapy, effectiveness was measured by relief of dysmenorrhea, pelvic pain, dyspareunia and decreasing induration of the cul-de-sac. (See adjoining table for clinical data to date on symptomatic relief with new Danocrine.)
Complete or partial relief in 89% of 226 patients with this symptom	
Complete or partial relief in 84% of 115 patients with this symptom	
Complete or partial relief in 82% of 185 patients with this sign	
Preliminary evidence suggests significant benefit in cases of infertility associated as a symptom of endometriosis††	

New Danocrine® brand of danazol usually offers dramatic relief from the symptomology caused by endometriosis

*See important prescribing information, including warnings, precautions, adverse reactions, patient selection, and dosage recommendations on last page.

†Data on file, Winthrop Laboratories.

††Follow-up studies are continuing.

Danocrine is indicated in those patients:

- who cannot tolerate other drugs.
- in whom other effective drugs are contraindicated.
- who fail to respond to adequate doses of other effective drugs.
- in whom surgery alone is considered not to be the treatment of choice.

Well-accepted

- Generally mild side effects profile—avoids the potentially serious hormonal effects of conventional high dosage estrogenic and progestational regimens.
- Non-estrogenic and non-progestational.
- No stimulating effect upon ectopic endometrial tissue.

Generally reversible antigonadotropic action

Generally, on completion of therapy, the antigonadotropic activity of Danocrine is reversed, resulting in a return of ovulation and cyclic menstrual bleeding within 60-90 days.

High degree of clinical success confirmed by laparoscopic photographs

Clinical trials with new Danocrine have indicated an efficacy and tolerability previously unattainable through pharmacological therapy. And therapy with Danocrine has the capability of resolving microscopic foci not amenable to surgical removal. In clinical trials to date,* complete or partial resolution of symptoms has been reported in 82-96% of 267 patients. In certain cases, these findings have been confirmed visually by laparoscopy and biopsy[1] (see photos).

Severe bilateral ovarian endometriomas



After 221 days of Danocrine therapy



Moderate unilateral ovarian endometrioma



After 189 days of Danocrine therapy



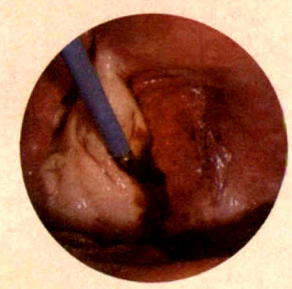
Left adnexal endometrioma



After 196 days of Danocrine therapy



Moderate pelvic endometriosis



After 227 days of Danocrine therapy



New Danocrine®

brand of

danazol

Now—a pharmacologic agent specifically for endometriosis

*Data on file, Winthrop Laboratories.

1. Dmowski, W.P. and Cohen, M.R.: Treatment of endometriosis with an antigonadotropin, Danazol: a laparoscopic and histologic evaluation, *Obstet. Gynecol.* 46:147, Aug. 1975.

See important prescribing information, including warnings, precautions, adverse reactions, patient selection, and dosage recommendations on

Danocrine®
Brand of danazol

Indications: Until additional studies have been completed which define the lowest clinically effective dose, Danocrine is indicated for the treatment of endometriosis amenable to hormonal management and only for those patients 1) who cannot tolerate other drug therapy, 2) in whom other effective drugs are contraindicated, or 3) who fail to respond to other effective drug therapy when given in adequate doses.

Danocrine is not indicated in those patients where surgery alone is considered the treatment of choice.

Contraindications: Danocrine should not be administered to patients with:

1. Undiagnosed abnormal genital bleeding.
2. Markedly impaired hepatic, renal, or cardiac function.
3. Pregnancy.
4. Breast feeding.

Warnings: Further studies are ongoing to define the lowest clinically effective dose of Danocrine. Consequently, at the present time, Danocrine should be limited in its use to the select group of patients mentioned in the *INDICATIONS* Section. In view of the fact that some cases of endometriosis may be resistant to one specific form of hormone therapy and responsive to another, Danocrine may prove to be of benefit in such cases. There are some limited data in support of the use of Danocrine in therapy-resistant cases of this type.

While no embryotoxic or teratogenic effects attributable to administration of Danocrine have been observed in reproduction studies in animals, safe use of the drug in pregnancy has not been established clinically. If a patient becomes pregnant during treatment, administration of the drug should be discontinued.

Patients should be watched closely for signs of virilization. Some androgenic effects may not be reversible even when drug administration is stopped.

Precautions: Because Danocrine may cause some degree of fluid retention, conditions that might be influenced by this factor, such as epilepsy, migraine, or cardiac or renal dysfunction, require careful observation.

Adverse Reactions: The following androgenic effects have occurred in patients receiving Danocrine: acne, edema, mild hirsutism, decrease in breast size, deepening of the voice, oiliness of the skin or hair, and weight gain.

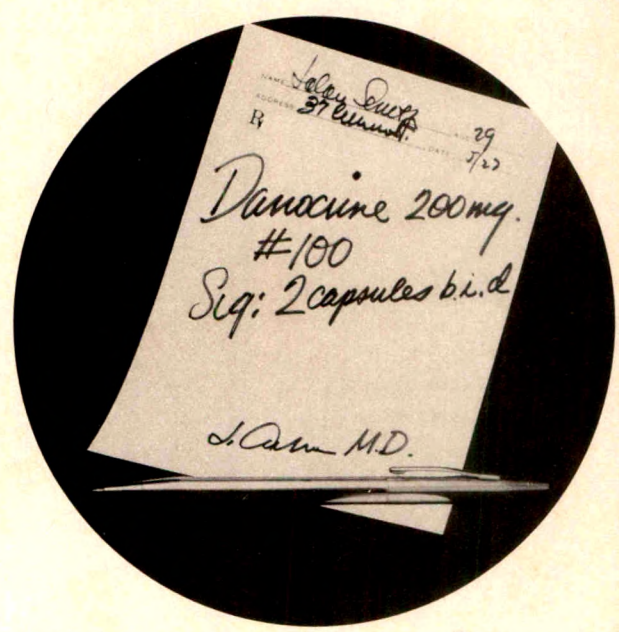
Also hypoestrogenic manifestations such as flushing, sweating, vaginitis including itching, dryness, burning and vaginal bleeding, nervousness, and emotional lability have been reported.

Although the following reactions have also been reported, a causal relationship to the administration of Danocrine has neither been confirmed nor refuted: *allergic*: skin rashes and rarely, nasal congestion; *CNS effects*: dizziness, headache, sleep disorders, fatigue, tremor, and rarely, paresthesia in extremities, visual disturbances, changes in appetite, and chills; *gastrointestinal*: gastroenteritis, and rarely, nausea, vomiting, and constipation; *musculoskeletal*: muscle cramps or spasms, and pain in back, neck, or legs; *genitourinary*: rarely, hematuria; *other*: loss of hair, changes in libido, elevation in blood pressure, and rarely, pelvic pain.

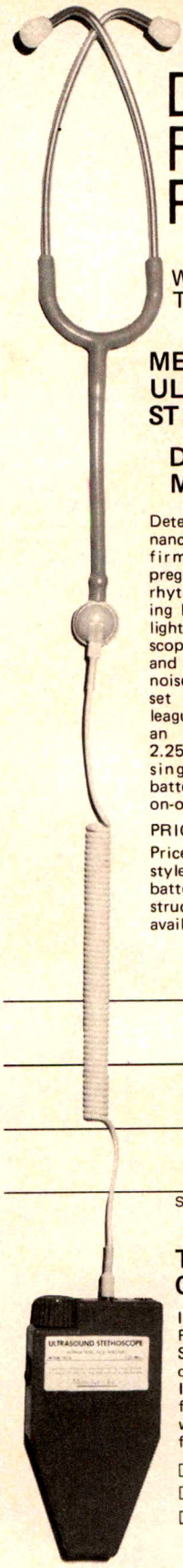
Dosage and Administration: The dosage of Danocrine is 800 mg., divided into two doses per day, until additional studies on the effectiveness of lower doses are completed. Therapy should continue uninterrupted for 3 to 6 months but may be extended to 9 months if necessary. After termination of therapy, if symptoms recur, treatment can be reinstituted.

How Supplied: Capsules of 200 mg. (orange), bottles of 100.

Winthrop Winthrop Laboratories, New York, N.Y. 10016
(1680M)



New Danocrine®
brand of
danazol
Now–a pharmacologic agent specifically for endometriosis



DETECT FETAL PULSE

WITH THE

MEDSONICS ULTRASOUND STETHOSCOPE®

Doppler Model FP3A

Detects fetal life early in pregnancy (9-12 weeks) • Confirms fetal life throughout pregnancy • Assesses rate and rhythm of the fetal heart during labor • Pocket size; small, light and durable • Stethoscope style headset for privacy and isolation from background noise • Jack for second headset permits patient or colleague to listen • Operates at an ultrasound frequency of 2.25 MHz • Powered by a single long-life, replaceable battery • Two simple controls; on-off switch and volume.

PRICE $375

Price includes one stethoscope style headset, carrying case, battery, coupling gel and instructions. Extra headset is available for $37.50.

NAME

ADDRESS

CITY

STATE ZIP CODE

TRY IT WITHOUT OBLIGATION

I wish to order the Model FP3A ULTRASOUND STETHOSCOPE fetal pulse detector. I understand that I may return the unit for full credit within two weeks after receipt if not fully satisfied.

☐BILL ME
☐CHECK ENCLOSED
☐ please send me more information.

MED SONICS

P.O. Box M, 340 Pioneer Way
Mountain View, California 94042
Telephone: (415) 965-3333

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

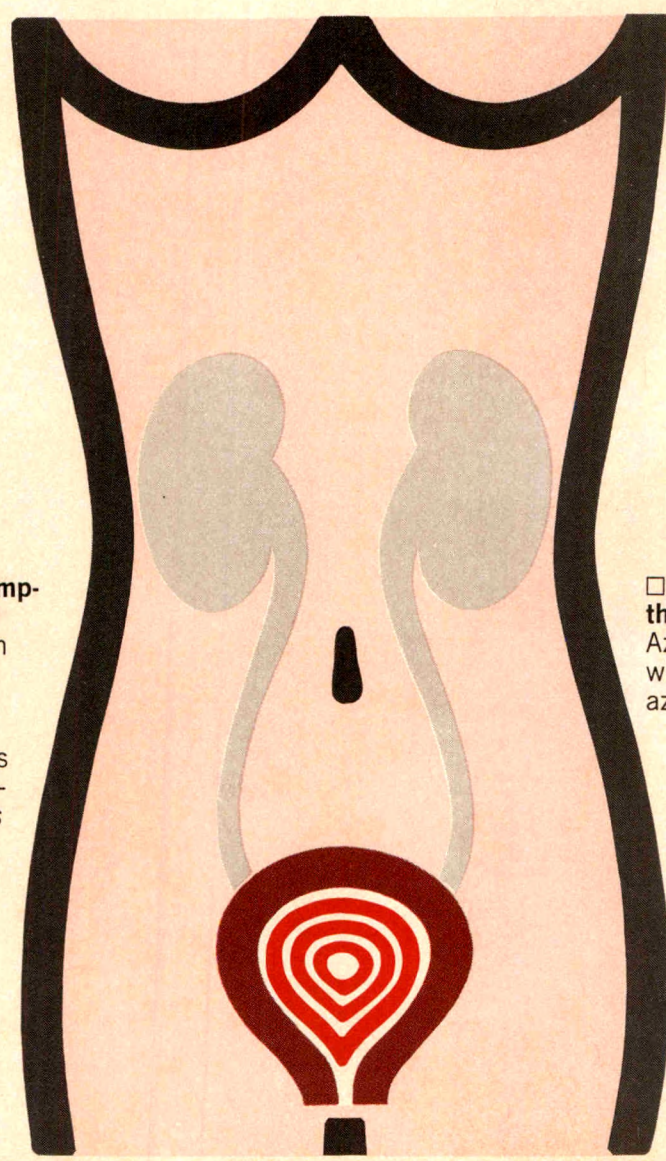
Roche Laboratories
Division of Hoffmann-La Roche Inc

When pain complicates acute cystitis*

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain for the pathogens



☐ **Early relief of painful symptoms** such as burning and discomfort associated with urgency and frequency.

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

☐ **Appropriate antibacterial therapy:** up to three days with Azo Gantanol, then 11 days with Gantanol® (sulfamethoxazole).

*nonobstructed; due to susceptible organisms

ROCHE





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials

Cycle	1	12	24	36	Total Cycles 20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment. *These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia.

3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll, R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. *3*:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 3 OCTOBER 1, 1976

CLINICAL OPINION

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to six citations. Mail to Frederick P. Zuspan, M.D., Editor.

Cigarette smoking, use of oral contraceptives, and myocardial infarction

ANRUDH K. JAIN, PH.D.

New York, New York

The excess risk of nonfatal myocardial infarction among users of oral contraceptives observed in England and Wales can be explained in terms of the high proportion of smokers in the study population. Among nonsmokers, the relative risk associated with the use of oral contraceptives is estimated to be 2 to 1, which is not statistically significant ($P = 0.28$, Fisher's exact probability test). The present analysis suggests that smoking be considered as another contraindication for the prescription of oral contraceptives. The results further indicate that those women who smoke as well as use oral contraceptives and are interested in reducing the risk of nonfatal myocardial infarction should be encouraged to give up smoking. The relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives observed in a society can vary between 0.9 to 1 and 11.7 to 1, depending upon the proportion of smokers. From the public health point of view, the reduction in the excess risk of nonfatal myocardial infarction achieved by eliminating smoking is estimated to be much more than can be achieved by eliminating the use of oral contraceptives.

From the Biomedical Division, The Population Council.

Supported in part by National Institutes of Health Grant No. Pol HD-0567 and undertaken as part of the contraceptive development research program sponsored and coordinated by the International Committee for Contraception Research of The Population Council.

Reprint requests: Dr. Anrudh K. Jain, Assistant Director, Biomedical Division, The Population Council, The Rockefeller University, York Ave. and 66th St., New York, New York 10021.

TWO CASE-CONTROL STUDIES conducted in England and Wales have indicated that the annual rate of nonfatal as well as fatal myocardial infarction among those women who use oral contraceptives is substantially higher than the corresponding rates among those women who do not use oral contraceptives.[1, 2] These excess risk estimates are quite likely to be generalized to assess the safety of oral contraceptives in other

countries. For examples, based on the results of these studies, the Food and Drug Administration had notified doctors in the United States " . . . that patients over 40 be made thoroughly aware of the increased risk and be urged to utilize other forms of contraception."[3] The purpose of this paper is to show that the generalizations of these excess risks to other countries or to different segments of the same country can be misleading unless the differences in other risk factors—especially the smoking habits of women—are taken into consideration. This is done by reanalyzing the data published in the above two studies. The results have far-reaching implications for making appropriate recommendations about the use of oral contraceptives to women in developed countries as well as for including them in the organized family planning programs around the world.

Nonfatal myocardial infarction

Mann and associates[1] have estimated that the relative risk of nonfatal myocardial infarction among women using oral contraceptive is 4.5 to 1 in comparison to those who never used oral contraceptives. This study was based on two of the 15 hospital regions in England and Wales. From the published data, the relative risk associated with the use of oral contraceptives can be estimated to be 3.0 to 1 in a third hospital region.[4] Note the regional variations in the relative risk estimates. Mann and associates[1] also estimated the incidence of nonfatal myocardial infarction among users and nonusers of oral contraceptives. However, these estimates were based on a study carried out in only one region. In view of the regional variations, it would hardly seem appropriate to generalize the estimates of incidences based on only one hospital region.

Our interest is to re-examine the association between the use of oral contraceptives and the risk of nonfatal myocardial infarction observed by Mann and associates[1] in two hospital regions. The main evidence seems to be that the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives decreased from 4.5 to 1 to 3.1 to 1 after the effects of other risk factors were considered. The standardization procedure mainly adjusts for the interrelationships between various factors. However, the magnitude of the standardized measure of association between the use of oral contraceptives and the risk of nonfatal myocardial infarction would depend upon the prevalence of other risk factors in the study population. This aspect of the relationship becomes quite important when the combined effect of two or more risk factors is synergistic. Therefore, it has to be shown that among those who are not exposed to any other risk factor the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives is statistically significant before the standardized relative risk can be accepted as an indicator of an actual association between the two. This association is not supported by the analysis that follows.

Effect of other risk factors. From the data published in Table X by Mann and associates,[1] it can be estimated that in comparison with women not known to have any risk factors the relative risk of nonfatal myocardial infarction in women using oral contraceptives alone is 1.5 to 1, which is one third of the relative risk estimated for all users. Moreover, the relative risk associated with the use of oral contraceptives alone is also smaller than the corresponding risks associated with other risk factors considered individually. For example, the relative risk associated with obesity alone can be estimated to be 3.9 to 1, and that associated with cigarette smoking alone can be estimated to be 3.5 to 1. The numbers are too small to draw any firm conclusion. Nevertheless, the results do indicate that the use of oral contraceptives alone does not appreciably increase the risk of nonfatal myocardial infarction.

The relevance of considering the interaction between the use of oral contraceptives and other risk factors for nonfatal myocardial infarction can be further demonstrated by analyzing the effect of smoking on the estimated relative risk associated with the use of oral contraceptives. For this purpose, the data published by Mann and associates[1] in their Table VIII are further analyzed.

Effect of smoking. It can be readily seen from the results presented in Columns 1 and 4 of Table I that the relative risk of nonfatal myocardial infarction among those who only use oral contraceptives is about the same as the relative risk among those who only smoke. The risks among women in these two groups are estimated to be about twice as high as those who neither use oral contraceptives nor smoke cigarettes. The relative risk associated with the use of oral contraceptive alone is not statistically significant ($P = 0.28$, Fisher's exact probability test) whereas the relative risk associated with smoking alone is statistically significant ($P = 0.029$, Fisher's exact probability test). The relative risk among those who use oral contraceptives as well as smoke is estimated to be 11.7 to 1. These comparisons indicate that the use of oral contraceptives alone does not significantly increase the risk of nonfatal myocardial infarction and the presence of both the risk factors simultaneously increases this risk about twelvefold.

The relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives among smokers can be estimated to be 5.4 to 1 (11.67 to 2.1[illegible]).

The corresponding risk associated with smoking among users can be estimated to be 5.8 to 1 (11.67 to 2.02). These comparisons indicate that, given smoking, the use of oral contraceptives substantially increases the risk of nonfatal myocardial infarction and, given the use of oral contraceptives, smoking substantially increases this risk. The increment in both cases is about the same.

Effect of heavy smoking. The heavy smokers, consisting of those who smoke 15 or more cigarettes per day, can be treated separately from the light smokers, consisting of those who smoke 14 or fewer cigarettes per day. The results in Table I indicate that in comparison to those who neither use oral contraceptives nor smoke cigarettes heavy smoking alone increases the risk of nonfatal myocardial infarction about fourfold, and heavy smoking along with the use of oral contraceptives increases this risk about fifteen times. Moreover, the relative risk associated with heavy smoking alone is about twice as high as the corresponding risk associated with the use of oral contraceptives alone (4.2 to 2.0 or 2.1 to 1). However, the difference is not statistically significant (P = 0.25, Fisher's exact probability test).

Incidently, based on the data published by Vessey and Doll,[5] Frederiksen and Ravenholt[6] estimated that in comparison to the risk in nonsmokers and nonusers the relative risk of thromboembolism in users who were also heavy smokers was 23 to 1. The corresponding relative risk among users and nonsmokers was 7.2 to 1 and among nonusers who were heavy smokers was 1.5 to 1. Thus, the combined effect of smoking and use of oral contraceptives on the risk of thromboembolism appears to be synergistic; smoking alone does not seem to elevate the risk appreciably but the use of oral contraceptives does seem to increase this risk substantially, even among nonsmokers.

Interaction between smoking and use of oral contraceptives. The relative risk associated with the use of oral contraceptives is the ratio of these risks among users and nonusers. These risks, in turn, are the weighted averages of the corresponding risks among smokers and nonsmokers—the weights being the proportion of smokers among users and nonusers. Thus, the relative risk associated with the use of oral contraceptives in a population consisting of smokers and nonsmokers can be estimated by using the proportion of smokers among users and nonusers and the relative risk estimates shown in Columns 1 and 4 of Table I. For example, in the control population of the British study, about 43 per cent of the users and 50 per cent of the nonusers were classified as smokers. With the use of these proportions and the relative risks shown in Columns 1 and 4 of Table I, the relative risk associated with the use of oral contraceptives in the total population can be estimated to be 6.16 to 1.58 or 3.9 to 1, instead of 4.5 to 1 which was estimated by Mann and associates.[1] The difference between the two estimates is due to the differences in the numbers in their Tables III, IV, and VIII.

The relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives can be standardized for smoking differences by assuming that the proportion of smokers among users is equal to the proportion of smokers among nonusers in the control

Table I. Estimated relative risks of nonfatal myocardial infarction by use of oral contraceptives and cigarette smoking

Smoking data	*Current user of oral contraceptives*	
	Yes	*No*
Smokers		
Total	11.67	2.15
Heavy*	14.81	4.23
Light†	5.38	0.77
Nonsmokers	2.02	1.00
Heavy smokers	16.21	4.63
Light smokers or nonsmokers	2.95	1.00
Smokers and nonsmokers	3.90	1.00

Based on data in Table VIII by Mann and associates.[1]
*Heavy smokers: at least 15 cigarettes per day.
†Light smokers: less than 15 cigarettes per day.

Table II. Estimated relative risks of nonfatal myocardial infarction as a function of proportion of smokers among current users and nonusers of oral contraceptives

Current user of oral contraceptives	*Per cent smokers (%)*	*Relative risks of nonfatal myocardial infarction*	
		*No. 1**	*No. 2†*
Yes	100	11.67	5.43
No	100	2.15	1.00
Yes	50	6.84	4.33
No	50	1.58	1.00
Yes	25	4.43	3.43
No	25	1.29	1.00
Yes	5	2.50	2.36
No	5	1.06	1.00
Yes	0	2.02	2.02
No	0	1.00	1.00

*In comparison to nonsmokers and nonusers.
†In comparison to all nonusers.

Table III. Estimated excess risk of nonfatal myocardial infarction attributable to smoking and use of oral contraceptives

Smoker	*User of oral contraceptives*	*1. Proportion of women*	*Incidence of nonfatal myocardial infarction*		*Components of excess risk*	
			2. Estimated	*3. Excess*	*4. Total*	*5. Relative*
Yes	Yes	0.0390	11.67*I	10.67*I	0.4161*I	41.96
Yes	No	0.4545	2.15*I	1.15*I	0.5227*I	52.70
No	Yes	0.0520	2.02*I	1.02*I	0.0530*I	5.34
No	No	0.4545	I	0	0	0
Total		1.000	1.99*I		0.9918*I	100.00

Column 1: Distribution of 154 women in the control population of the British study.[1] Column 2: Table I—I is the incidence of nonfatal myocardial infarction among nonusers and nonsmokers. 1.99*I = Σ Column 1 *Column 2. Column 3: = Column 2 − I. Column 4: = Column 1 *Column 3. Column 5: $= \frac{\text{Column 4}}{0.9918*I} * 100$.

group of the British study. Standardization for smoking slightly increases the relative risk associated with the use of oral contraceptives from 3.9 to 1 to 4.3 to 1. This slight increase can be explained in terms of a small negative correlation (−0.041) between the use of oral contraceptives and smoking in the control group of the British study.

Mann and associates[1] presumably standardized the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives for heavy smoking. For this purpose, the light smokers and nonsmokers are to be treated together. In the control group of the British study, about 28.6 per cent of the users were heavy smokers as compared to 20 per cent of the nonusers. Standardization for the differences in heavy smokers reduces the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives from 3.9 to 1 to 3.2 to 1. A small reduction in the relative risk is observed because of the small correlation (0.061) between the use of oral contraceptives and heavy smoking observed in the control group of the British study. The reduction would have been much greater than that observed had the correlation between heavy smoking and the use of oral contraceptives been higher than 0.061.

Interestingly, these results can also be used to show that heavy smoking also substantially increases the risk of nonfatal myocardial infarction and that the increase is independent of the use of oral contraceptives. In the control group of the British study, about 12.5 per cent of the heavy smokers and about 8.2 per cent of the rest used oral contraceptives. With the use of these proportions and the relative risk estimates in Columns 5 and 6 of Table I, the relative risk of myocardial infarction among heavy smokers can be estimated to be 5.2 to 1 in comparison with the rest. This ratio is reduced to 4.8 to 1 after the differences in the proportion of users among heavy smokers and the rest are standardized.

Depending upon the interest in the search for a causal factor of myocardial infarction, the results of the same study could be used to show that the use of oral contraceptives, independent of smoking, is associated with an increased risk of nonfatal myocardial infarction. Alternatively, the results of the same study could also be used to show that smoking, independent of the use of oral contraceptives, is associated with an increased risk of nonfatal myocardial infarction. The latter interpretation is accurate because the relative risk of nonfatal myocardial infarction associated with smoking is statistically significant, even among nonusers of oral contraceptives. However, the former interpretation of the results is incomplete and misleading because among nonsmokers the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives is not statistically significant.

Effect of proportion of smokers. The relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives observed in a population will depend upon: (1) the association between the use of oral contraceptives and smoking, and (2) the proportion of smokers among users and nonusers. To illustrate these points, the relative risks estimated from the British study shown in Columns 1 and 4 of Table I are considered.

First, consider a population in which all users and none of the nonusers smoke cigarettes. In this population, the relative risk associated with the use of oral contraceptives would be observed to be 11.7 to 1. Second, consider another extreme situation—a population in which none of the users and all nonusers smoke cigarettes. In this population, the relative risk associ-

ated with the use of oral contraceptives would be observed to be 0.9 to 1. In both cases, these relative risks standardized for the differences in proportion of smokers would be 2 to 1, because, in both cases, the standardization procedure would assume that none of the users as well as none of the nonusers smoke cigarettes.

Consider a third population in which there is no correlation between the use of oral contraceptives and smoking. In this population, the relative risk associated with the use of oral contraceptives will depend upon the proportion of smokers, because the combined effect of smoking and the use of oral contraceptives is synergistic.

The proportion of women who smoke cigarettes does vary between different countries. For example, in developing countries like India, Pakistan, and Bangladesh, very few women smoke cigarettes. For illustrative purposes, the over-all risks associated with the use of oral contraceptives as a function of the proportion of smokers are shown in Table II. It can be readily seen that the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives in a country could vary between 2.0 to 1 and 5.4 to 1, depending upon the proportion of smokers among users and nonusers.

The results presented above clearly indicate that the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives observed in the British study can be explained in terms of the proportion of smokers in the study population and the fact that the combined effect of smoking and use of oral contraceptives is synergistic. This aspect of the complex relationship was obscured in the standardization procedure used in the British study.

Excess risk attributable to smoking and use of oral contraceptives. Let I be the incidence of nonfatal myocardial infarction among nonusers of oral contraceptives who do not smoke. This incidence in the total population of the British study can be estimated to be 1.99*I. In other words, smoking and the use of oral contraceptives increases the incidence of nonfatal myocardial infarction by about 99 per cent. This excess risk can be partitioned in various components that can be attributed to smoking and the use of oral contraceptives separately. The results are presented in Table III. It can be seen that about 53 per cent of the excess risk can be attributed to smoking alone; about 42 per cent, to smoking and the use of oral contraceptives; and only 5 per cent of the excess risk of nonfatal myocardial infarction can be attributed to the use of oral contraceptives alone. In other words, 95 per cent of the excess risk can be attributed to smoking as compared to 47 per cent attributable to the use of oral contraceptives.

Table IV. Estimated relative risk of death from myocardial infarction among different categories of use of oral contraceptives

Use of oral contraceptives	*Age of patients*	
	30-39 years	*40-44 years*
"Never users"	1.00	1.00
Current users	3.36	4.38
24 months or less	1.91	2.19
25 months or more	5.06	6.57
Exusers	2.18	0.55
"Ever users"	2.92	1.82
"Never users" and exusers	1.00	1.00
Current users	2.80	4.55

Based on data in Tables II and III from Mann and Inman.[2]

If smoking is completely eliminated, then the excess risk can be estimated to be 0.093*I—a reduction of about 91 per cent from the present level. On the other hand, if the use of oral contraceptives is completely eliminated, then the reduction in the excess risk can be estimated to be about 42 per cent, from 0.99*I to 0.57*I. Thus, from the public health point of view, the excess risk of nonfatal myocardial infarction in a society can be reduced considerably by eliminating smoking rather than by eliminating the use of oral contraceptives.

Fatal myocardial infarction

The data are not available to analyze the relative risks of fatal myocardial infarction associated with the use of oral contraceptives separately among smokers and nonsmokers because Mann and Inman[2] were not able to obtain the data on smoking habits of their study population. However, it is doubtful that the results for fatal myocardial infarction for smokers and nonsmokers separately would be substantially different than the results for nonfatal myocardial infarction, especially in view of the fact that among all users of oral contraceptives the relative risks of fatal myocardial infarction have been shown to be similar in magnitude to the corresponding risks of nonfatal myocardial infarction.[1, 2]

Incidently, the estimates of relative risks of fatal myocardial infarction associated with the current use of oral contraceptives could be an artifact of the distinction between the current users and the exusers. The following analysis indicates that this especially may be the case for women 40 to 44 years of age.

The results presented in Table IV indicate that for the current users the relative mortality risks in women 40 to 44 years of age are higher than the corresponding relative risks in women 30 to 39 years of age whereas for the exusers the relative mortality risk in women 40 to 44 years of age is lower than that in women 30 to 39 years of age. This is quite puzzling, and one may be tempted to attribute the differences to small numbers.

At the same time, other possibilities cannot be ruled out. It is possible that some of the exusers in the 40 to 44 year age group might have been classified as current users. There is no way to ascertain whether or not women actually used oral contraceptives during the month before death except by interviewing them but one cannot interview those who died! This is a complicated problem having no unique solution. One may be tempted to combine the exusers with the current users for estimating the relative risks. However, this approach would also bias the results, because the time when the exusers stopped using oral contraceptives is not known. It may be one month, six months, one year, or more before death. Furthermore, the duration for which the exusers used oral contraceptives also is not known, and the duration of use among current users seems to be associated with the relative mortality risk of myocardial infarction (see Table IV).

The relative mortality risks in the "ever users" of oral contraceptives in comparison to "never users" in the 30 to 39 year age group is quite close to the corresponding estimate for the current users. However, for the "ever users" in the 40 to 44 year age group, the estimate is substantially lower than that for the current users. The closeness of the two estimates for the 30 to 39 year age group and the difference in these estimates for the 40 to 44 year age group indicate that there might be some problem in the latter age group in classifying women as current or exusers. This may have artificially elevated the mortality risk associated with the use of oral contraceptives in women of 40 to 44 years of age.

Implications

For properly assessing the association between the use of oral contraceptives and myocardial infarction, it is essential to understand the complex interactive effects of smoking, age of the woman, and the use of oral contraceptives. For this purpose it is imperative that the relative risks of fatal and nonfatal myocardial infarction associated with the use of oral contraceptives are separately estimated for smokers and nonsmokers within each age group. Moreover, the durations of use and nonuse of oral contraceptives need to be taken into consideration, especially for the risk of fatal myocardial infarction. These types of analysis ought to be carried out in future studies of this nature.

The results of the present analysis, though limited in scope, have clear implications for women using oral contraceptives.

1. The results of British studies cannot be generalized to women in other countries without consideration of their smoking habits.

2. There seems to be no evidence to suggest that the use of oral contraceptives alone significantly increases the risk of nonfatal myocardial infarction. The relative risk associated with the use of oral contraceptives alone is 1.5 to 1 in comparison with the risk in women not known to have any other risk factor and 2 to 1 among nonsmokers, which is not statistically significant and is less than 4.5 to 1, estimated by Mann and associates[1] for all users. It is quite likely that a similar relationship will hold for women 30 to 39 years of age as well as for those 40 or more years of age. However, a firm conclusion in this regard cannot be reached without further analysis.

3. There is strong evidence to suggest that the combined effect of smoking and use of oral contraceptives on the risk of nonfatal myocardial infarction is synergistic. Moreover, the relative risk of nonfatal myocardial infarction associated with smoking is statistically significant even among nonusers of oral contraceptives. These results indicate that those women who smoke as well as use oral contraceptives and want to reduce the risk of nonfatal myocardial infarction should be encouraged to give up smoking. Smoking, in other words, should be considered as another contraindication for the prescription of oral contraceptives. This may especially apply to women over 40 years of age. However, it is quite likely that the relationship may hold even for women 30 to 39 years of age. A firm conclusion cannot be reached without further analysis.

4. It is possible that the above conclusions may not hold for the risk of fatal myocardial infarction, but this seems quite unlikely in view of the similarity in magnitudes of relative risks of fatal and nonfatal myocardial infarction associated with the use of oral contraceptives among all users. Moreover, the estimated mortality risk among users 40 to 44 years of age may have been artificially elevated because of some inaccuracy in classifying them as current users.

This paper has greatly benefited from the comments and suggestions of Sushil Kumar, Dale Robertson, and Irving Sivin.

REFERENCES

1. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial infarction in young women with special reference to oral contraceptive practice, Br. Med. J. **2:** 241, 1975.
2. Mann, J. I., and Inman, W. H. W.: Oral contraceptives and death from myocardial infarction, Br. Med. J. **2:** 245, 1975.
3. FDA Drug Bulletin 5:10 (DHEW Publication No. [HEW] 393), Food and Drug Administration, Rockville, Maryland, July-August, 1975.
4. Mann, J. I., Thorogood, M., Waters, W. E., and Powell, C.: Oral contraceptives and myocardial infarction in young women: A further report, Br. Med. J. **3:** 631, 1975.
5. Vessey, M. P., and Doll, R.: Investigation of relationship between use of oral contraceptives and thromboembolic disease. A further report, Br. Med. J. **2:** 651, 1969.
6. Frederiksen, H., and Ravenholt, R. T.: Thromboembolism, oral contraceptives, and cigarettes, Public Health Rep. **85:** 197, 1970.

OBSTETRICS

The effect of active immunity against placental proteins on pregnancy in monkeys

JOHN P. GUSDON, JR., M.D.

With the technical assistance of

CANDACE C. WITHEROW

Winston-Salem, North Carolina

Squirrel monkeys were actively immunized against human placental lactogen (HPL) and/or an extract of human placental tissue, or squirrel monkey placenta. Only half of the monkeys immunized with HPL developed a detectable antibody titer to HPL prior to the subsequent mating season. During the subsequent breeding season, the pregnancy rate was cut in half. The titer developed against HPL did not seem to be related to their ability to become pregnant. When the group of animals which had previously been immunized with HPL were challenged with extracts of human placenta, all animals developed detectable circulating antibody. There was no increase in the effectiveness of this immunization as compared to HPL in pregnancy prevention, however. A third group of monkeys was immunized with extracts from their own placental extracts, and all developed some degree of antibody. The titer obtained did not seem to be related to whether or not they became pregnant. In this group, however, the pregnancy rate was decreased to one fourth of what it had been before immunization.

NONE OF THE various methods of contraception and sterilization available to us today meets the needs and requirements of all groups of peoples. Therefore, continued efforts to develop and test new methods are warranted. The possibility that immunization might be feasible as a method of pregnancy control in the female is based upon the fact that trophoblast is antigenic and, under experimental conditions, antibodies have been produced in both homologous and heterologous systems.[1–5] There is a wealth of published data on placental and embryonic antigens recently succinctly reviewed by Coggin and Anderson.[6] The possibility that these kinds of antigens might play a role in the development of a contraceptive immunologic response has been explored previously by a number of individual investigators,[7–10] only a few of whom are cited. The possible significance of this approach is attested to by the fact that it formed the basis for a World Health Organization Meeting in 1974.[11]

Although in previous studies from this laboratory, we have been successful in preventing any deliveries of pregnancies by the administration of heterologous anti-human placental lactogen (HPL) to rats,[9] the methodology of achieving that result is not feasible for use in the human subject. These studies were initiated in monkeys because they are more closely related to the human being and the results could be, therefore, more

From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine.

This research was supported by a grant from the Rockefeller Foundation.

Received for publication December 12, 1975.

Revised March 5, 1976.

Accepted March 5, 1976.

Reprint requests: John P. Gusdon, Jr., M.D., Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103.

meaningful. The development of a contraceptive vaccine would meet the requirement of a large group of people, if proved to be both safe and effective. The present study was undertaken in an effort to test the hypothesis that antibodies against placental proteins could provide an effective means of contraception.

Materials and methods

Animals. Squirrel monkeys were used for these studies. Four groups of monkeys containing at least eight females per group at the onset of the study were followed for a period of 5 years. These animals were all housed as separate colonies in identical quarters as part of a national resource for squirrel monkeys, at the Bowman Gray School of Medicine farm. The housing provided was standard for all groups and included both indoor and outdoor facilities. The food was standard. Two groups (Groups A and B), each with eight females and one male, received no treatment of any kind and formed a control group. The females of two other groups (C and D), each having eight females and one male, and identical in all other ways to Groups A and B, were immunized against HPL prior to their third observed reproductive year.

In this way, the immunized animals' reproductive ability could be compared to their own prior history, as well as that of a comparable group that was not immunized. The group was then immunized with an extract of human placenta (HPE) in an effort to determine if immunization to a multiplicity of antigens which might be unique to pregnancy and the placenta would be more effective in depressing the reproductive ability of these animals than was obtained with one relatively pure placental antigen in the preceding season. Another colony of different composition (12 females and one male) but identical in all other respects was also followed; initially they were observed as a control group. Prior to the fifth observed year these animals were immunized against an extract of squirrel monkey placenta. This group is designated as Group E. The reproductive capacity of this group was well known, and the effect of immunization against homologous placental antigens could be determined.

Antigens.

*A. HPL 717-340.** This was alum-precipitated and 5 mg. were injected subcutaneously into the medial aspect of each thigh of all females in Groups C and D in February of the third observed year, in an effort to obtain immunization prior to the onset of the spring mating season. Each monkey received injections every other week for a total dosage of 30 mg. of alum-precipitated HPL. In an effort to enhance the possible development of cell-mediated immunity, 2 months after the first series of injections, each of these animals was given 2 mg. of Poly A: Poly U* intravenously 1 day prior to the subcutaneous injection of 10 mg. of AP-HPL.[12]

B. Human placental extract. A normal human placenta obtained from a term delivery was drained of as much blood as possible, the membranes were excised, and the trophoblast was minced and then homogenized. A 3M KCl extract was then made of these tissues, with the use of a slight modification of the methods described by Meltzer and associates.[13] Homogenization was done in a Sorvall omni-mixer with three times the volume (w/v) of 3M KCl in 0.005M potassium phosphate buffer, pH 7.4, for 3 to 4 minutes, until adequate tissue disruption was obtained. Mixing was continued at 4° C. for 16 to 24 hours after which the mixture was centrifuged at 20,000 g for 90 minutes. The supernatant was collected and dialyzed against 20 volumes of deionized water for 60 minutes at 4° C. with each tissue. The dialysate was again centrifuged for 30 minutes at 20,000 g, the supernatant fraction was dialyzed against 20 volumes of 0.1M NaCl for 60 minutes, and the protein concentration was determined by biuret.[14] The extract was filter sterilized, alum-precipitated, and prior to the fourth mating season used for immunization of all females in Groups C and D. Each monkey received 5 mg. of alum-precipitated extract subcutaneously into each thigh once a week for 4 weeks.

The total extract of membrane-associated proteins derived from both the human and monkey placentas contains a multiciplicity of different proteins. No attempt was made to separate these proteins prior to their use. It was hoped that a comparison between the effects of a pure placental protein, HPL, and the total extracts could be obtained.

C. Squirrel monkey placenta extract. Because the monkeys usually ate their placentas immediately after a birth, it was necessary to deliver two monkeys at term by cesarean section, to obtain placental tissue. These monkeys were from the same large colony maintained at the Bowman Gray School of Medicine. These placentas were extracted in the same manner as outlined for the human placentas above. All 12 Group E females were immunized against the monkey placental extract with 5 mg. of alum-precipitated extract per thigh each week for 4 weeks before the mating season.

*Kindly supplied by Dr. P. H. Bell, Lederle Laboratories, Pearl River, New York, and stated to be 95 per cent pure.

*Polyadenylic acid–polyuridilic acid, Miles Laboratory, Inc., Kankakee, Illinois.

Table I. The effect of immunization with heterologous and homologous placental products upon subsequent pregnancy

	Viable pregnancies delivered				
*Group**	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
A	7/8†	7/8	7/8	8/8	7/7‡
B	7/8	7/8	8/8	6/7‡	5/7
C	7/8	7/8	4/8§	2/7§	3/7
D	7/8	8/8	4/7‡§	2/7§	2/7
E	11/12	10/12	10/12	9/12	3/12§

*A and B, matched control groups; C and D, immunized X HPL 717-340 prior to year 3 and human placental extract (HPE) prior to year 4; E, immunized against monkey placental extract prior to year 5.

†The number of viable births/the number of females in the group.

‡One nonpregnant animal died from pneumonia prior to the end of this reproductive cycle.

§Immunized prior to that mating season.

Antibody assays. Hemagglutination procedures were carried out on all monkey sera after the last injections of antigen prior to the mating season. The methodology utilized has been described previously.[15] One hundred micrograms of monkey or human placenta extract protein were used per milliliter of 2.5 per cent cells for the sensitization of the formalinized cells for the titration of antibody by hemagglutination. Blood was obtained 10 days after the last injection of any immunogen, and the serum was separated and stored at −20° C. until used for assays. This was done in Groups C and D in years 3 and 4. However, since the animals were not immunized prior to the fifth observed breeding season, they were simply bled in February, serum extracted, and then studied for both anti-HPL and anti–human placental extract serum titers. Sera were also obtained from monkeys immunized against the extract of squirrel monkey placenta on the tenth day after the last injection prior to the fifth observed mating season.

Results

The reproductive history of all groups is presented in Table I. The antibody titers found in each animal in Groups C and D prior to each respective mating season are presented in Table II. Only one half of the monkeys immunized with HPL developed an antibody titer to it prior to the third year, whereas all the animals developed an antibody to HPE in the fourth year. The response to HPL was minimal. The level of antibody produced against placental antigens was greater. However, the incidence rate of pregnancy, though higher in the absence of detectable antibody, does not reach statistical significance. The incidence rate of pregnancy in the fourth and fifth years is not significantly changed from the third year in these two groups.

In Table II we have outlined the incidence rates of pregnancies in all five groups of monkeys. With the use of Fisher's exact test, a significant decrease in the incidence of pregnancy ($P = <0.025$) is seen comparing Groups C and D, which were immunized, to either A and B throughout, or E in the first 4 years of study of that group. In the latter, immunization was not accomplished in the first 4 years. The same level of significance is achieved by comparing the third, fourth, and fifth years of Groups C and D to their first 2 years of observation. As can be noted in Table II, no titers were found prior to the fifth mating season of Groups C and D. However, the depression of the birth rate persisted. It is also of interest to note, in Table II, that two animals which had previously failed to deliver in the third year did so in the fourth year. This seemed to have been balanced by the fact that two of the monkeys which had delivered during the preceding season failed to do so in the fifth season, although untreated. Group E, after immunization with squirrel monkey placental extract prior to the fifth years of observation, showed a significant ($P = <0.025$) depression of pregnancy. Immunization led to a decreased ability to reproduce, but this suppression was not absolute. As in Groups C and D, the presence of a positive titer against the squirrel monkey placental extract did not preclude pregnancy. All animals had been injected three times with alum-precipitated squirrel monkey placental extract and, on the tenth day after the last injection, they were bled. The monkeys all had titers varying from 1/16 to 1/64. The three animals which delivered babies had titers of 1/32 (two) and 1/64 (one).

Comment

The data presented here show that active immunization with either homologous or heterologous placental proteins does result in a significant decrease in effective reproduction. However, it appears that the use of neither HPL nor extracts of placental tissues resulted in a complete suppression of reproduction. Of some interest is the fact that several animals which seem to have been prevented from successful reproduction by the procedure of immunization against the placental proteins did become pregnant in the following mating season when reimmunization was not instituted. This suggests that if indeed the active immunization was responsible for the failure to reproduce, then continued successful contraception by this method might require repeat immunization procedures. This might

Table II. Antibody titers and their relationship to subsequent pregnancy

		Year 3		Year 4		Year 5	
Group	*Monkey No.*	*Titer HPL**	*Subsequent pregnancy§*	*Titer PE†*	*Subsequent pregnancy*	*Titers‡*	*Pregnancy*
C	1	10	0	512	0	0	0
	2	0	+	64	+	0	+
	3	0	+	64	+	0	+
	4	0	0	32	0	0	0
	5	20	0	18	0	0	0
	6	10	+	16	0	0	0
	7	20	0	32	0	0	0
	8	0	+	Died	—	—	—
D	1	0	0	64	0	0	0
	2	10	0	128	0	0	+
	3	0	+	64	0	0	+
	4	0	+	Died	—	—	—
	5	40	0	512	+	0	0
	6	20	+	256	0	0	0
	7	20	0	16	+	0	0
	8	0	+	16	0	0	0

*Reciprocal of the hemagglutination titer obtained 10 days after immunization with HPL prior to the third observed reproductive season.

†Reciprocal of the hemagglutination titer obtained 10 days after the last injection of human PE prior to the fourth observed reproductive season.

‡Reciprocal of the hemagglutination titers of sera obtained in February preceding the fifth observed reproductive season against HPL and PE.

§0 means that no pregnancy occurred in that reproductive season; + means that a pregnancy and delivery of a viable infant occurred in that reproductive season.

be an advantage to the individual who is interested in temporary contraception, but a distinct disadvantage to the person who requires permanent sterilization. The parameters which would result in either one or the other result are not defined in this study. The success attained (failure to reproduce) in this study was incomplete. It is also noteworthy that the actual titer of antibody attained is not absolutely related to whether or not a pregnancy ensued. It is possible that this might be the result of measuring only one arm of the multitude of immunologic responses to antigenic stimulation. We have not yet developed methods for testing the cell-mediated immune responses of these animals to these antigens. We were able to measure only the production of antibodies in response to stimulation with these placental antigens. It should be pointed out that the presence of specific placental antigen(s) in rhesus and squirrel monkeys has been described recently by Behrman and associates.[16] They indicated that studies which they have done, in collaboration with Bohn,[17] have shown that their antigen cross-reacts with a human placental antigen which he has designated as SPl. No studies have been done by us to determine what role these antigens might have, if any, in the results we have obtained.

The utilization of a mixture of membrane proteins derived from the human placenta was accomplished in an attempt to determine if a greater degree of success could be achieved by the use of all extractable antigens. This hoped-for result was not attained. It is possible that these antigens could be presented to the host in a different form or manner, and by such modification, and immune response of killer T lymphocytes rather than B cells could result. Some of these studies are underway. Our inability to elicit any antibody production in half of the animals, and only very low levels in the other females, might also be the result of the close structural relationship of this protein hormone in the human being and the monkey. This kind of relationship of proteins in the placenta has been shown to exist by the study of Behrman and associates[16] and the SPl human placental protein of Bohn.[17] Stevens[10, 18, 19] anticipated this kind of problem and modified gonadotropin by coupling it with a hapten. As a result of the structural modification which he was able to attain, the modified gonadotropin molecule was an excellent immunogen. A significant enhancement of antigenicity was attained and he and his co-workers were able to disrupt ovulation patterns in baboons. In a discussion at a symposium on immunologic approaches to fertility control, Stevens[10] presented data on the use of the beta subunit of HCG to immunize sheep, rabbits, and baboons. In 30 matings in 10 baboons of proved fertility (90 percent), no pregnancies which might have

occurred lasted longer than a normal cycle. These data are far superior to the results obtained in this study. It would seem that active immunization against a small portion of a protein, which is unique to the placenta, is quite effective in the prevention of pregnancy.

Those of us who are involved in attempts to prevent pregnancy by immunization against trophoblast-specific antigens must constantly bear in mind a possible dangerous side effect. The antibody which we induce by the injection of these antigens might allow a spontaneously developing malignancy to continue its existence by blocking the cell-mediated immune response which would otherwise destroy the tumor. In the process of development, any given cell in the body has the genetic capability to become any other cell and thereby synthesize any protein. Subsequent cellular differentiation then involves a process that selectively turns off synthetic capabilities until, at the final differentiated stage, we have only the mature cells with limited functions. In a malignancy, there is a derepression of the genome, and a resultant re-expression of embryonic synthetic capabilities. We must take care that in our attempts to manipulate the immune response to prevent pregnancy, we do not prevent the immune surveillance system from seeing that embryonic antigens arising from a malignancy are present.

REFERENCES

1. Cohen, H. R., and Nedzel, J. A.: Specific action of an antiserum for placental proteins on placenta and normal progress of pregnancy, Proc. Soc. Exp. Biol. Med. **43:** 249, 1940.
2. Seegal, B. C., and Loeb, E. N.: Effect of anti-placenta serum on development of foetus in pregnant rat, Proc. Soc. Exp. Biol. Med. **45:** 248, 1940.
3. Pressman, D., and Korngold, L.: Localizing properties of anti-placenta serum, J. Immunol. **78:** 75, 1957.
4. Hulka, J. F., Hsu, K. C., and Bieser, S. M.: Antibodies to trophoblasts during the postpartum period, Nature (Lond.) **191:** 510, 1961.
5. Koren, Z., Abrams, G., and Behrman, S. J.: The role of host factors in mouse trophoblastic tissue growth, Am. J. Obstet. Gynecol. **100:** 570, 1958.
6. Coggin, J. H., and Anderson, N. G.: Cancer differentiation and embryonic antigens: Some central problems, Ad. Cancer Res. **19:** 106, 1974.
7. Glass, R. H., and Mroueh, A.: Pregnancy in the rabbitt following immunization with human chorionic gonadotropin, Am. J. Obstet. Gynecol. **97:** 1082, 1967.
8. El Tomi, A. E. F., Crystle, C. D., and Stevens, V. C.: Effects of immunization with human placental lactogen on reproduction in female rabbits, Am. J. Obstet. Gynecol. **109:** 74, 1971.
9. Gusdon, J. P., Jr.: An immunologic method of pregnancy destruction and contraception, Am. J. Obstet. Gynecol. **112:** 472, 1972.
10. Stevens, V. C.: Immunization of female baboons with hapten-coupled gonadotropins, Obstet. Gynecol. **42:** 496, 1973.
11. Diczfalusy, E., editor: Karolinska Symposia on Research Methods in Reproductive Endocrinology. Symposium 7: Immunological Approaches to Fertility Control, held in Geneva, 1974, Acta Endocrinol. **78:** 1975.
12. Cone, R. E., and Johnson, A. G.: Regulation of the immune system by synthetic polynucleotides. IV Amplification of proliferation by thymus-influenced lymphocytes, Cell. Immunol. **3:** 283, 1972.
13. Meltzer, M. S., Leonard, E. J., Rapp, H. J., and Borsos, T.: Tumor specific antigen solubilized by hypertonic potassium chloride, J. Natl. Cancer Inst. **47:** 703, 1971.
14. Mokrasch, L. C., and McGilvery, R. W.: Purification and properties of fructose-1,6′-Diphosphatase, J. Biol. Chem. **221:** 909, 1956.
15. Gusdon, J. P., Jr., Leake, N. H., and Burt, R. L.: Naturally occurring antibody to placental protein in human pregnancy, Obstet. Gynecol. **37:** 90, 1971.
16. Behrman, S. J., Yoshida, T., Amano, Y., and Paine, P.: Rhesus and squirrel monkey placental specific antigen(s), Am. J. Obstet. Gynecol. **118:** 616, 1974.
17. Bohn, H.: Nachweis and Charakterisie rung von löslicken Antigenen in der menschlichen Placenta, Arch. Gynäkol. **212:** 165, 1972.
18. Stevens, V. C., and Crystle, C. D.: Effects of immunization with hapten-coupled HCG in the human menstrual cycle, Obstet. Gynecol. **42:** 485, 1973.
19. Stevens, V. C.: Fertility control through active immunization using placenta proteins, *in* Diczfalusy, E., editor: Karolinska Symposia on Research Methods in Reproductive Endocrinology Symposium 7: Immunological Approached to Fertility Control, held in Geneva, 1974, Acta Endocrinol. **78:** 368, 1975.

Human uterine artery responses to lidocaine

CHARLES P. GIBBS, M.D.

STEPHEN C. NOEL, PH.D.

Gainesville, Florida

Uterine arteries from pregnant and nonpregnant patients were studied to define their responses to lidocaine. Although local anesthetics usually are considered vasodilators, these data indicate that the human uterine artery constricts when exposed to 1,000 μg of lidocaine in vitro. Furthermore, those arteries from pregnant patients exhibitied significantly greater responses than did those from nonpregnant patients.

ALTHOUGH LOCAL anesthetics are usually considered vasodilators,[1–4] there are reports indicating that they can be vasoconstrictors.[5–7] How the pregnant human uterine artery responds to local anesthesia is unknown. Therefore, the response of these arteries to a commonly used local anesthetic, lidocaine hydrochloride, was investigated.

Methods

Six term uterine arterial segments were obtained from cesarean hysterectomy specimens, and seven segments were obtained from nongravid specimens. No patients were hypertensive, nor were any taking hormonal or autonomic drugs. The patients were receiving various anesthetic agents including Pentothal, nitrous oxide, halothane, enflurane, fentanyl-droperidol, morphine and meperidine when the vessels were obtained. The ages of the nongravid patients ranged from 29 to 36 years. All were still menstruating.

The arterial segments were taken from an area as close to the uterus as possible and immediately placed in a beaker of Krebs-Henseleit solution. The specimens were gently divested of surrounding fat and connective tissue and tubular rings approximately 3 to 4 m.m. long were removed from the segments. The rings were allowed to stablize for one-half hour in the Krebs-Henseleit solution through which oxygen (95 per cent) and carbon dioxide (5 per cent) were bubbled. They then were mounted on two stainless steel wires. One of the wires was attached to a Narco biosynthesis force transducer; the other was attached to a supporting rod. The equipment, similar to that used by Fay and Cooke,[8] is used to measure isometric contractions generated by the arterial ring (Fig. 1). Once mounted, the segments again were allowed to equilibrate with the surrounding oxygen-carbon dioxide Krebs-Henseleit solution. After equilibration, a baseline tension of 500

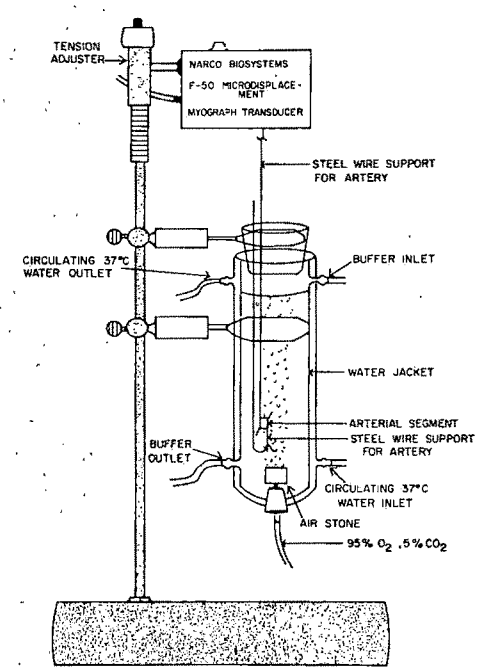


Fig. 1. Waterbath and myograph transducer as arranged for measurement of isometric arterial muscle contraction.

From the Departments of Anesthesiology and Obstetrics and Gynecology, University of Florida College of Medicine, J. Hillis Miller Health Center.

This research was supported in part by Seed Money from the Division of Sponsored Research, University of Florida.

Received for publication September 22, 1975.

Revised January 13, 1976.

Accepted January 30, 1976.

Reprint requests: C. P. Gibbs, M.D., Department of Anesthesiology, University of Florida College of Medicine, Box J-254, J. Hillis Miller Health Center, Gainesville, Florida 32610.

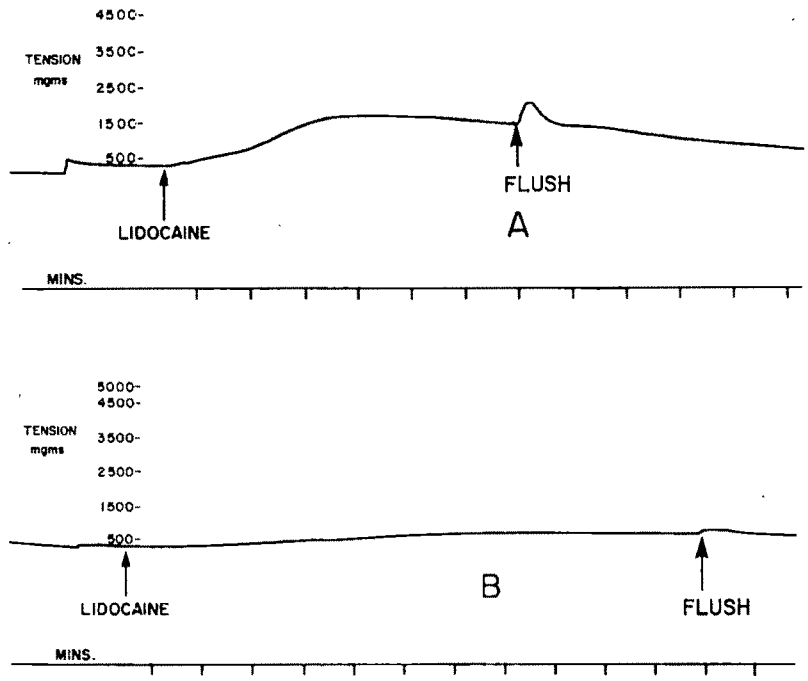


Fig. 2. Recording of response of pregnant *(A)* and nonpregnant *(B)* uterine artery to 1,000 μg per milliliter of lidocaine.

Table I. Tension produced by isometric contractions of uterine artery exposed to 1,000 μg per milliliter of lidocaine (tension represents the difference between baseline tension and maximum tension attained)

Pregnant patient	*Tension (mg./100 ml.)*	*Nonpregnant patient*	*Tension (mg./100 ml.)*
1	2,650	7	725
2	4,300	8	0
3	4,750	9	2,100
4	2,000	10	400
5	1,500	11	0
6	1,350	12	1,650
		13	0
Mean	2,758.3*		696.4*
±S.E.	±591.4		±324.0

*P < 0.01.

mg. was placed on the arterial segments. One thousand μg per milliliter of lidocaine without perservative or epinephrine was then added to the bath, and the developed isometric tension for each segment was recorded on a Narco biosynthesis polygraph. When the developed tension became maximal, the bath was emptied of the solution containing the local anesthetic and flushed two to three times with buffer. The flushing allowed the arterial tension to return to baseline.

Results

All arterial segments from the pregnant specimens contracted to this dose of lidocaine whereas only four of the seven nonpregnant arteries contracted (Table I). The milligrams of tension reported represent the difference between the baseline tension and the maximum tension attained. The tension developed by arteries from pregnant uteri was significantly greater than that from nonpregnant uteri (Student's unpaired t test) ($P < 0.01$). Typical responses of both groups are presented in Fig. 2. Very little spontaneous activity was seen in any specimen.

Comment

The present data indicate that the in vitro human uterine artery will constrict in the presence of lidocaine and that arteries from pregnant uteri allow a significantly greater response than those from nonpregnant uteri. Why uterine arteries contract to lidocaine when most other vessels relax[1–4] is unknown. There are, however, reports of other vessels contracting to local anesthetics. Lidocaine constricts lobar venous vessels of the lung in intact dogs[5] and causes venoconstriction of cat and rat anterior mesenteric veins.[6] Lidocaine also causes forearm venoconstriction, and mepivacaine has produced forearm arterial constriction. Therefore, some vessels do constrict to local anesthetic,[7] and the uterine artery appears to be one of these.

Why the pregnant artery reacts more than the non-

pregnant one is also unknown. The answer may simply be that the gravid vessel is larger and, therefore, capable of stronger contractions. Pregnancy, or an altered hormonal environment, also has been shown to alter factors which influence vascular reactivity. Debreczeni and Takacs[9] noted that nonpregnant and pregnant rats differ in their responses to alpha- and beta-blocking agents. Sjoberg[10] found that he could increase the amount of neuronal norepinephrine in the uterus and blood vessels by pretreating nonpregnant rabbits with 17-beta estradiol. Furthermore, Bell,[11] utilizing perfused guinea pig uterine arteries, found that a norepinephrine-induced contraction could be relaxed by electrical periarterial stimulation in the pregnant but not the nonpregnant animal. More pertinent was his finding that the vasodilation produced by the electrical stimulation in the pregnant animal is abolished by local anesthetics. Quite recently Morishima and co-workers[12] have demonstrated that intravenous administration of lidocaine to maternal sheep decreased uterine blood flow. These results could indicate that the uterine artery was constricting in response to the lidocaine.

Clinically, these results may indicate another possible cause for the fetal bradycardia associated with paracervical block. Since paracervical block bradycardia is usually associated with low fetal blood levels of anesthetic,[13, 14] the 1,000 μg per milliliter used in this study may not be applicable. However, the usual paracervical block techniques utilized injections of 10 c.c. of 1 per cent lidocaine on each side. This amount represents a total dose per side of 100,000 μg. Therefore, the uterine artery may be exposed to 1,000 μg or more of the local anesthetic.

Further studies are needed to determine how lidocaine acts on the uterine vessels and to determine whether all local anesthetics produce these same effects. Most importantly, animal studies are needed to determine if these in vitro results can be duplicated in vivo.

REFERENCES

1. deJong, R. H.: Physiology and pharmacology of local anesthesia, Springfield, Ill., 1970, Charles C Thomas, Publisher, p. 147.
2. Altura, B. M., and Zweifach, B. W.: Pharmacologic properties of antihistamines in relation to vascular reactivity, Am. J. Physiol. **209:** 550, 1965.
3. Altura, B. M.: Evaluation of neurohumoral substances in local regulation of blood flow, Am. J. Physiol. **212:** 1447, 1967.
4. Nishimura, N., Morioka, T., Sato, S. et al.: Effects of local anesthetic agents on the peripheral vascular system, Anesth. Analg. **44:** 135, 1965.
5. Hyman, A. L.: The effects of lidocaine, hexamethonium and alpha and beta adrenergic blocking agents on the pulmonary veins in intact dogs, J. Pharmacol. Exp. Ther. **174:** 487, 1970.
6. Sanders, H. D.: Procaine-induced contraction in vein and its modification by drugs, Can. J. Physiol. Pharmacol. **47:** 218, 1969.
7. Jorfeldt, L., Lofstrom, B., Pernow, B. et al: The effect of mepivacaine and lidocaine on forearm resistance and capacitance vessels in man, Acta Anaesthesiol. Scand. **14:** 183, 1970.
8. Fay, F. S., and Cooke, P. H.: Guinea pig ductus arteriosus. II. Irreversible closure after birth, Am. J. Physiol. **222:** 841, 1972.
9. Debreczeni, L. A., and Takacs, L.: The effect of phenoxybenzamine and propranolol on the circulation of pregnant rats, *in* Betz, E., editor: Vascular smooth muscle, New York, 1972, Springer-Verlag, p. 102.
10. Sjoberg, N. O.: Increase in transmitter content of adrenergic nerves in the reproductive tract of female rabbits after oestrogen treatment, Acta Endocrinol. **57:** 405, 1968.
11. Bell, C.: Dual vasoconstrictor and vasodilator innervation of the uterine arterial supply in the guinea pig. Circ. Res. **23:** 279, 1968.
12. Morishima, H. O., Heymann, M. A., Rudolph, A. M. et al: Transfer of lidocaine across the sheep placenta to the fetus, AM. J. OBSTET. GYNECOL. **122:** 581, 1975.
13. Jordan, H. R.: Fetal bradycardia after paracervical block, N. Engl. J. Med. **217:** 910, 1968.
14. Arling, T. H., Shnider, S. M., Margolis, A. J. et al: Paracervical block anesthesia in obstetrics, AM. J. OBSTET. GYNECOL. **107:** 626, 1970.

Repeat aborters

SANDRA M. SCHNEIDER
DOUGLASS S. THOMPSON
Pittsburgh, Pennsylvania

In an attempt to learn more about the phenomenon of repeat abortions, 116 women seeking a repeat abortion were compared in various ways with three groups of women not seeking a repeat abortion but otherwise similar. From this study it is apparent that postabortion women become, over time, less persistent users of contraception than sexually active nonpregnant women. However, they are more likely to use contraception continually than are women seeking a first abortion. The abortion experience, with or without concurrent family-planning guidance, does not create universally sufficient long-lasting motivation to use of contraception. Some other factors which might contribute to this motivation are presented.

THE CONTINUING liberalization and acceptance of induced abortion in the United States has raised many concerns about repeat induced abortions. Aside from moral and ethical considerations, there is growing apprehension about the possible late clinical sequelae of such abortions such as increases in the incidence of prematurity,[1] cervical incompetence,[2, 3] ectopic pregnancy,[4] secondary sterility,[5] and Rh immunization.[6] If any or all of these increases occur, it becomes even more important for repeat unwanted pregnancies to be prevented rather than aborted.

It perhaps is reasonable to hope that this prevention will occur because having an unwanted pregnancy terminated by an abortion would seem to be an excellent and long-lasting stimulus for contraception. Generally less than 50 per cent of women use contraception at the time of the conception that precedes their first abortion as indicated by several studies.[7–9] Thereafter, the percentage of these postabortion women who use contraception seems to increase substantially. Athanasiou and co-workers[8] reported that 70 per cent of women claimed to be using the pill or the IUD more than one year after abortion. Still another study indicated that, 6 months after abortion, 74 per cent of the women were using the pill or IUD, 4 per cent had been sterilized, and only 9 per cent were sexually active without contraception.[10]

However, regardless of what they do or do not do about contraception, all sexually active, or potentially active, fertile women who have had one or more abortions are at risk of having another unwanted pregnancy for which they might seek a repeat abortion. Repeat abortions are not rare, as is noted in Table I. Since, at least in the past, some abortion services did not accept repeat aborters, some women desiring repeat abortions may not have sought them, thus artificially lowering the percentages noted in this literature. An analysis of the likelihood of repeat abortions, presented by Tietze,[23] was not optimistic about the situation. As the number of women at risk of having repeat abortions increases, the number and rate of repeat abortions seems destined to increase. Tietze,[23] making various assumptions, predicted that within 10 years after their first abortion 100 postabortion pill users will have had 20 to 70 repeat abortions and that 100 postabortion users of other contraception will have had 100 to 300 abortions.

It has been suggested that those women who are not using contraception after an abortion are depending on abortion as an alternative to contraception and that women seeking a repeat abortion come primarily from this group. However, Bracken, Hachamovitch, and Grossman[18] in studying repeat aborters, found that they were more likely to have used contraception at the time of conception than were first-time aborters (50 per cent versus 32 per cent). They concluded that repeat aborters are more likely to be victims of contraceptive failures for one reason or another than to be

From the Department of Medicine and Department of Obstetrics and Gynecology, University of Pittsburgh School of Medicine.

Received for publication December 15, 1975.

Accepted February 25, 1976.

Reprint requests: Dr. D. S. Thompson, Magee-Womens Hospital, Pittsburgh, Pennsylvania 15213.

using abortion as an alternative to contraception. Rovinsky[19] concluded similarly. However, the comparison group in these and other similar studies has always been first-time aborters. Such a comparison group is not an ideal one to use in trying to assess how much repeat aborters consider abortion to be their contraception.

In an effort to learn more about the phenomenon of the repeat abortion, we felt it would be helpful to study repeat aborters at abortion services which are known to accept repeat aborters and to compare them with groups other than first aborters. We also felt that the repeat aborters could be compared among themselves with respect to postabortion contraceptive counseling, depending on the circumstances of their previous abortion(s). Therefore, we undertook the following study.

Materials and methods

Four populations of women were studied via a questionnaire: (1) those who were seeking a repeat abortion, (2) those who were seeking their first abortion, (3) those who currently were continuing a pregnancy, and (4) those presumably at risk of conception who were not pregnant. The first and second populations (aborters) were patients at two hospitals, neither of which prohibited repeat abortions, during an 18 month period. The third population was from a group of women, all at various stages of pregnancy, at the prenatal clinic in one of these hospitals. The final population, all not pregnant, came from two different groups. The first group were women, amenorrheic for 2 or more weeks, concerned about pregnancy and self-requesting pregnancy tests, which later were reported as negative, at one of these hospitals. The other group were family-planning patients attending a local family-planning clinic.

The questionnaires were self-administered and were anonymous. They were completed by the abortion seekers prior to the abortion and were not made available to the service providers and thus were not part of their decision making. The remaining populations completed the questionnaire during a 6 month period. Information derived from the questionnaire included age, marital status, previous pregnancies, previous induced abortions (with identification as to whether these were legally performed in a hospital or clinic or illegal "street" abortions), and contraceptive use in the past year, at the time of conception for those pregnant or, for those not pregnant, within the last month, and intended future contraception. Of the 1,924 women who completed the questionnaire, 116 (6.0 per cent) were repeat aborters.

Table I. Repeat induced abortions or abortion requests in the United States and abroad

Country or state	*Year*	*Per cent of women having repeat induced abortion within 1 year*	*Per cent of women applying for abortion with history of previously induced abortion*
Russia[11]	1958-59	15	—
Hungary[11]	1960	12	—
	1965	17	—
Sweden[12]	1955	15	—
Japan[13]	1971	—	32.2
U. S./ Kansas[14]	1960	—	30
U. S.[15]	1971	—	14.6
U. S./New York[16–19]	1970-72	5-7.4	—
U. S.[20]	1969	—	24.6
U. S./ Boston[21]	1968-70	—	9
U. S./ Hawaii[22]	1972	1.1	—

Results

Repeat aborters compared with themselves. The histories of repeat aborters included both legal abortions and illegal or "street" abortions (Table II). The contraceptive use of those who had had only legal abortions and of those who had had only illegal abortions prior to the sought abortion at two points in time and as intended in the future is shown in Table III. While contraception was used frequently prior to conception and intended for the future, many of these women had discontinued contraception at the time of conception. This was particularly true, interestingly, of the nonpermanent coitally unrelated methods (pill, IUD). There was a lesser discontinuance of the coitally related methods. There were, of course, contraceptive failures among both groups. Ryder reported "method" plus "people" contraceptive failures over a 1 year period of 7 per cent for women initially using the pill and 15 per cent for women initially using the IUD.[24] It does not seem at all surprising to find that so many women, having had one or more abortions already, seek another when experiencing an unwanted pregnancy subsequent to a contraceptive failure. Table III also shows that there is no statistically significant difference ($P = 0.5$) in the use of contraceptives at any time between the two groups even though the group receiving legal abortions presumably had received contraceptive counseling of some sort whereas those receiving illegal abortions probably had not.

A well-recognized variable in contraceptive use is the age of the woman. Table IV utilizes the same breakdown of types of contraceptives as above, but compares

Table II. Repeat aborters giving histories of past legal and/or illegal abortions

No. of previous abortions	Repeat aborters		Repeat aborters having had: Only legal abortions		Only illegal abortions		Both legal and illegal abortions	
	No.	%	No.	%	No.	%	No.	%
1	96	83	67	70	29	30		
2	12	10	6	50	5	41	1	8
3	5	4	3	60	0		2	40
4	2	2	0		1	50	1	50
5	1	1	1	100	0		0	
Totals 147	116	100	77	100	35	30	4	4

Table III. Contraceptive use by repeat aborters: Legal vs. illegal abortions

Contraceptive	Per cent (rounded) of repeat aborters using contraception: N112* In past year (%) Legal (N = 77)	In past year (%) Illegal (N = 35)	At time of conception (%) Legal (N = 77)	At time of conception (%) Illegal (N = 35)	Intended in future (%) Legal (N = 77)	Intended in future (%) Illegal (N = 35)
Coitally unrelated	48	49	19	9	94	97
Pill	32	42	3	6	31	28
IUD	14	6	12	3	33	35
Sterilization	1	0	4	0	29	35
Coitally related†	40	33	41	24	4	0
None	13	18	41	67	0	3
Totals	100	100	100	100	100	100

*Four "repeaters" who had both legal and illegal abortions are not included.
†Diaphragm, foam, condom, douche, rhythm, withdrawal.

their usage according to four age groupings. The percentage of women using contraception rises generally with age until the woman is over age 35.

Repeat aborters compared to the other sexually active women. Each repeat abortion woman was matched with a woman in each of the other three populations by the criteria of parity (excluding previous induced abortions), marital status, and age (plus or minus 1 year). Matching was done by selecting the first woman in each of the nonrepeat abortion populations who met the criteria of the repeat aborter with whom she was to be matched.

We then compared the four matched groups regarding their use of contraception in the past year, at the time of conception for those pregnant or within the last month for those not pregnant, and regarding the method of contraception intended for the future (Table V). This again shows that a majority of women, including those who were receiving prenatal care, were using contraception during the past year.

However, there was a statistically significantly higher use of coitally unrelated contraception during the past year by repeat aborters as compared with first aborters and pregnant women ($P = 0.01$), but not between the repeat aborters and the nonpregnant women. There was also a statistically significant higher use of any type of contraceptive at the time of conception by the repeaters than by the first time aborters or by the pregnant women ($P = 0.01$). However, the repeaters had used contraception less frequently at the time of the conception than had the nonpregnant women within the month prior to completing the questionnaire.

Comment

This and other studies indicate that women who have had an abortion increase their use of contraception thereafter and remain more likely to use it than do women who are about to have a first abortion. This study also indicates that women who have had an abortion use contraception more than women who are continuing a pregnancy but less than do a group of sexually active nonpregnant women. If our assumption is correct, and we believe it to be, that women who had illegal abortions got little or no family-planning counseling from their aborters, we must conclude that the stimulus toward greater use of contraception subsequent to abortion comes more from the abortion

Table IV. Contraceptive use by repeat aborters by age

	Per cent (rounded) of repeat aborters using contraception: N-116								
	In past year			*At time of conception*			*Intended in future*		
Age (yr.)	*CU* (%)*	*CR* (%)*	*None (%)*	*CU (%)*	*CR (%)*	*None (%)*	*CU (%)*	*CR (%)*	*None (%)*
15-20 (N = 18)	40	33	27	18	24	59	100	0	0
21-25 (N = 51)	56	32	12	18	38	44	97	0	3
26-35 (N = 39)	51	41	8	14	30	57	100	0	0
36- (N = 8)	13	75	13	0	75	25	80	20	0

*CU = Coitally unrelated. CR = Coitally related.

Table V. Contraceptive use by women having repeat abortions (R); first abortions (F); continuing pregnancy (P); and not pregnant (N), all Ns: 116

	Per cent (rounded) of women using contraception											
	In past year (%)				*At time of conception* (%)*				*Intended in future (%)*			
Contraceptive	*R*	*F*	*P*	*N*	*R*	*F*	*P*	*N*	*R*	*F*	*P*	*N*
Coitally unrelated	49	30	34	66	15	4	17	58	98	89	72	85
Pill	(36)	(24)	(22)	(49)	(4)	(2)	(9)	(43)	(30)	(39)	(41)	(61)
IUD	(12)	(6)	(12)	(17)	(9)	(3)	(9)	(14)	(40)	(31)	(19)	(21)
Sterilization	(1)	(0)	(0)	(0)	(3)	(0)	(0)	(1)	(28)	(19)	(12)	(4)
Coitally related	38	41	22	21	36	39	18	18	1	8	13	11
None	13	29	46	13	49	57	65	23	1	2	15	4
Totals	100	100	100	100	100	100	100	100	100	100	100	100

*Or during the month prior to answering the questionnaire for those not pregnant.

experience than from counseling by the aborters since their use of contraception is not significantly different from those who had had legal abortions and, presumably, counseling by their aborters.

However, the major points appear to be that (1) there are a sizable number of women who have had and will have repeat abortions; (2) these women's use of contraception, especially coitally unrelated contraception, reaches its maximum immediately after abortion and falls off thereafter; and (3) these women's use of contraception at the time of their conceptions just prior to their repeat abortions is less than that of sexually active nonpregnant women. We cannot conclude from this study whether many of these repeaters tend to turn to abortion as a substitute for contraception. Undoubtedly, some, but probably not many, do, consciously or subconsciously. However, they apparently are not only victims of contraceptive failure, as suggested by Bracken, Hachamovitch, and Grossman,[18] but also they are less likely to use contraception than are nonpregnant (at the moment), sexually active women.

The high rates of use of contraception (which can be called an attempt to achieve immunity against a disease called unwanted pregnancy) by women immediately after recovering from this disease is a well-recognized social and medical phenomenon. Immunization activity always is highest in the face of personally threatening endemics or epidemics. As this threat diminishes, the immunization activity and rates drop off greatly over time. Thus, to maintain population immunity for this disease, motivation toward use of contraception must be stimulated continually so long as that contraception is something other than sterilization. But even continued motivation along with contraceptive use will be imperfect, of course. A recent study found that 34 per cent of couples who do not want another pregnancy and who are contracepting will have an unwanted pregnancy within 5 years.[24]

Of course, repeat unwanted pregnancies have been present for centuries and used to lead to many unwanted children and some illegal abortions. Now they lead to many legal abortions and some unwanted children. We simply do not know enough about preventing repeat unwanted pregnancies. Women having repeat unwanted pregnancies need special assistance and extra and special motivation to avoid them. Those women who have an unwanted pregnancy and who "cure" it by having a therapeutic abortion remain at high risk of having another unwanted pregnancy. It appears that they are inherently less able to prevent unwanted pregnancies than are some other groups of

women. Just what kind of assistance can be helpful is not known. Certainly it must be something different from what it has been and must be more than general family-planning education and counseling. The reasons why some women choose not to use contraception are complex and include denial, guilt, game playing, and fear.[26] Some have an overwhelming motivation for pregnancy.[26] It would seem to require, at a minimum, specific and individualized therapy and guidance.

Recognizing times and life circumstances ("stages") when women in general and, almost certainly, women who have had one or more abortions are especially vulnerable to an unwanted pregnancy can be helpful. Miller[27] discussed these "stages" which include changes in the relationship with a sexual partner, geographic motility, and various factors relating to marriage. The contribution of the partners of these women to their unwanted pregnancies may well be significant but is totally unknown.

Conclusions

There are a small but still substantial number of women who will continue to have unwanted pregnancies, even after one or more induced abortions. The reasons are complex and the usual and current preventive approaches are ineffective.

REFERENCES

1. Klinger, A.: Demographic consequences of the legalization of induced abortion in Eastern Europe, Int. J. Gynecol. Obstet., **8:** 680, 1970.
2. Wright, C. S. W., Campbell, S., and Beazley, J.: Second-trimester abortion after vaginal termination of pregnancy, Lancet **1:** 1278, 1972.
3. Forster, F. M. C.: Abortion and the incompetent cervix, Med. J. Aust. **2:** 807, 1967.
4. Panayotou, P. P., Kaskarelis, D. B., Miettinen, O. S., Trichopoulos, D. B., and Kalandidi, A. K.: Induced abortion and ectopic pregnancy, AM. J. OBSTET. GYNECOL. **114:** 507, 1972.
5. Pantelakis, S. N., Stefanos, G. C., and Doxiadis, S. A.: Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies, AM. J. OBSTET. GYNECOL. **116:** 799, 1973.
6. Ascari, W.: Abortion and maternal Rh immunization, Clin. Obstet. Gynecol. **14:** 625, 1971.
7. Daily, E. F., Nicholas, N., Nelson, F., and Pakter, J.: Repeat abortion in New York City: 1970-72, Fam. Plann. Perspect. **5:** 89, 1973.
8. Athanasiou, R., Oppel, W., Michelson, L., Unger, T., and Yager, M.: Psychiatric sequelae to term birth and induced early and late abortion: A longitudinal study, Fam. Plann. Perspect. **5:** 227, 1973.
9. Lerner, R. C., Bruce, J., Ochs, J. R., Wassertheil-Smoller, S., and Arnold, C. B.: Abortion programs in New York City: Services, policies and potential health hazards, Milbank Mem. Fund Q. **52:** 30, 1974.
10. Margolis, A., Rindfuss, R., Coghlan, P., and Rochat, R.: Contraception after abortion, Fam. Plann. Perspect. **6:** 56, 1974.
11. David, H. P.: Abortion in psychological perspective, Am. J. Orthopsychiatry **42:** 61, 1972.
12. Ekblad, M.: Induction abortion on psychiatric grounds. A follow-up study of 470 women, Acta Psychiatr. Scand. (Suppl.) **99:** 238, 1955.
13. Wagatsuma, T.: The abortion program in Japan, J. Reprod. Med. **7:** 16, 1971.
14. Wall, L. A.: Abortions: Ten years' experience at Kansas University Medical Center, AM. J. OBSTET. GYNECOL. **79:** 510, 1960.
15. Tietze, C., and Lewitt, S.: Early complications of abortion under medical auspices: A preliminary report, Stud. Fam. Plann. **2:** 137, 1971.
16. Rovinsky, J.: Abortion in New York City. Preliminary experience with a permissive statute, Obstet. Gynecol. **38:** 333, 1971.
17. Hall, R. E.: Induced abortion in New York City: A report of six separate studies, AM. J. OBSTET. GYNECOL. **110:** 601, 1971.
18. Bracken, M. B., Hachamovitch, M., and Grossman, G.: Correlates of repeat induced abortions, Obstet. Gynecol. **40:** 816, 1972.
19. Rovinsky, J.: Abortion recidivism, Obstet. Gynecol. **39:** 649, 1972.
20. Lee, N. H.: Search for an abortionist, Chicago, 1969, University of Chicago Press.
21. Barnes, A. B., Cohen, E., Stoeckle, J. D., McGuire, M. T.: Therapeutic abortion: Medical and social sequelae, Ann. Intern. Med. **75:** 881, 1971.
22. Kumbe, K. T.: Abortions among women on public assistance in Hawaii: Implications for practice, Am. J. Public Health **62:** 1538, 1972.
23. Tietze, C.: The problem of repeat abortions, Fam. Plann. Perspect. **6:** 148, 1974.
24. Ryder, N. B.: Contraceptive failure in the United States, Fam. Plann. Perspect. **5:** 133, 1973.
25. Sandberg, E. C., and Jacobs, R. I.: Psychology of the misuse and rejection of contraception, Med. Aspects Hum. Sexual. June, 1972, p. 34-70.
26. Marinoff, S. C.: Contraception in adolescents, Pediatr. Clin. North Am. **19:** 811, 1972.
27. Miller, W. B.: Psychological vulnerability to unwanted pregnancy, Fam. Plann. Perspect. **5:** 199, 1973.

Fetal immune response following prematurely ruptured membranes

LARS L. CEDERQVIST, M.D.
LINDA C. FRANCIS, B.S.
IOANNIS A. ZERVOUDAKIS, M.D.
CARL G. BECKER, M.D.
STEPHEN D. LITWIN, M.D.
New York, New York

Concentrations of immunoglobulins (Ig)A_1, and IgA_2, IgD, IgE, IgG, and IgM have been determined in cord blood, amniotic fluid, and maternal serum in a group of patients with a history of prematurely ruptured membranes (PRM) prior to the onset of labor and in a control group of patients undergoing normal delivery and without a history of infection during pregnancy. IgA and IgD were determined by sensitive hemagglutination-inhibition tests; IgG and IgM, by radial immunodiffusion; IgE, by a radioimmunoassay. There was evidence for an immune response in 10 of 16 cases of PRM: five of 16 had increased IgA but normal IgM; three of 16 had increased IgA and IgM; two of 16 had high IgM and normal IgA in cord blood. In patients with significantly increased levels of either IgA or IgM or both, there was a decreased level of IgD. These changes are most likely the result of the immune response to ascending infection from the maternal genitals. The sensitive testing method employed could demonstrate the presence of IgD in 53 per cent of normal cord blood samples and 72 per cent of amniotic fluid samples obtained at term. IgE was found in all normal cord blood and amniotic fluid samples tested. By concentrating the amniotic fluid up to 180-fold, IgM was demonstrated in all normal samples tested. The potential importance of IgA determinations in cord blood in addition to IgM determination for detection of intrauterine infections is stressed.

THE USEFULNESS OF immunoglobulin determinations of cord blood as an adjunct to the diagnosis of clinically inapparent and atypical neonatal infections, which may have serious sequelae later in life, has been well established.[1] Immunoglobulin (Ig)M in cord blood is reported to be frequently increased in congenital infections but not in all cases.[2] Both the type and the severity of the congenital infection determine the degree of IgM elevation.

Chorioamnionitis, as a result of an ascending infection from the vagina, may develop if the fetal membranes rupture prior to the onset of labor. Most often, the infection is limited to the amniotic cavity, and the fetus becomes infected passively by swallowing or aspirating the exudate. The fetus does not always become infected, even in the presence of extensive chorioamnionitis.[3] On the other hand, certain infections of the maternal genital tract consistently result in a high incidence of serious or even fatal infections of the fetus after only a short history of prematurely ruptured membranes (PRM) prior to the onset of labor. For example, in a recent study of 10 patients who had documented herpes simplex virus infection of the vulva and PRM for over four hours, there were five neonatal deaths and three surviving infants with severe neurological deficits.[4]

We have recently presented evidence, by using ge-

From the Departments of Obstetrics and Gynecology and Microbiology and the Division of Human Genetics, Department of Medicine, The New York Hospital–Cornell Medical Center.

This work was made possible by a grant from The National Foundation–March of Dimes and was partially supported by United States Public Health Service Grants A1-09239 and AM-202122.

Received for publication August 22, 1975.

Accepted February 24, 1976.

Reprint requests: Dr. Lars L. Cederqvist, Department of Obstetrics and Gynecology, The New York Hospital–Cornel Medical Center, 525 E. 68th. St., New York, New York 10021.

Table I. Immunoglobulin levels in maternal serum (MS), cord blood (CB), and amniotic fluid (AF) obtained at delivery from patients with a history of PRM and from a normal control group

Immunoglobulin	*Sample*	*Control group*		*PRM group*		*Significance*
		No.	*mg./dl.*	*No.*	*mg./dl.*	
IgA	MS	34	313 ± 212	16	401 ± 270	
	CB	36	1.8 ± 0.9	17	9.2 ± 16.3	$p < 0.1$
	AF	36	4.3 ± 2.2	6	4.7 ± 2.1	
IgA_1	MS	34	265 ± 166	16	313 ± 211	
	CB	36	1.6 ± 0.9	17	7.8 ± 13.4	$p < 0.1$
	AF	36	3.7 ± 2.2	6	3.5 ± 1.0	
IgA_2	MS	34	40 ± 28	16	39 ± 27	
	CB	36	0.3 ± 0.3	17	1.0 ± 3.0	
	AF	36	0.5 ± 0.4	6	0.5 ± 0.4	
IgD	MS	34	15 ± 17	16	22 ± 26	
	CB	36	0.5 ± 1.1	17	0.1 ± 0.1	$p < 0.05$
	AF	36	0.15 ± 0.29	6	0.13 ± 0.06	
IgG	MS	34	799 ± 358	16	847 ± 390	
	CB	36	572 ± 316	17	545 ± 255	
	AF	36	17 ± 13	6	16 ± 5	
IgM	MS	34	152 ± 60	16	167 ± 60	
	CB	36	8.2 ± 5.4	17	12.7 ± 7.8	$p < 0.05$
	AF	27	0.3 ± 0.4	6	0.4 ± 0.8	
IgE	MS	33	321 ± 306*	15	433 ± 716*	
	CB	26	108 ± 130*	13	70 ± 70*	
	AF	22	7 ± 5*	4	9 ± 9*	

No. refers to the number of samples tested. Significance was determined between the control group and the PRM group by Student's t test in unpaired samples.

*Nanograms per milliliter.

netic typing of IgA_2, that the fetus can synthesize IgA in utero.[5] Fetal IgA_2 could be detected as early as 14 weeks of gestation in cord blood and amniotic fluid, which showed a high fraction of IgA_2/IgA_1 until late gestation. The purpose of this present study was to examine a group of patients with PRM to determine whether an immune response, involving IgA and its two subgroups IgA_1 and IgA_2, occurs. Correlative data are also presented on IgD, IgE, IgG, and IgM in cord blood, amniotic fluid, and maternal serum.

Material and methods

The sera, cord blood, and amniotic fluid (if available at the time of delivery) from 16 mothers with a history of PRM between the thirty-third and forty-first weeks of gestation were tested for IgA, IgA_1 and IgA_2 subgroups, IgD, IgE, IgG, and IgM. The results were compared with data obtained from 36 patients who had a normal delivery at term with no evidence of infection during pregnancy.

IgA and its subgroups IgA_1 and IgA_2 were semiquantiatively measured by inhibition of hemagglutination tests.[5] Human O+ red blood cells were coated with IgA_1 (Crip) and IgA_2 (Bra) myeloma proteins by the chromic chloride method.[6] The following rabbit (R) antisera were used: R 463 anti-IgA, R 414 anti-IgA_1, and R 404 anti-IgA_2. Antisera were absorbed with serum from an IgA-deficient patient, and specificity was confirmed by inhibition by a panel of myeloma proteins of known classes and types. To measure IgA or its subgroups, serial dilutions of amniotic fluid or fetal or maternal serum in 10 μl volumes were mixed with 10 μl of antiserum in V-shaped wells in a microtiter plate.*[7] After 30 minutes of incubation at 4° C., 10 μl of the appropriate washed immunoglobulin-coated cells was added to each well, and the microtiter plate was incubated for one hour at room temperature. The plate was centrifuged for 30 seconds at 2,000 r.p.m. (805 g) in an International Model PR-2 centrifuge and then left standing for 20 minutes at a 60° angle before being read. Test samples were always read along with the IgA_1 and IgA_2 standards, myeloma proteins Coh and La. A preselected antiserum dilution was used which caused moderate agglutination of immunoglobulin-coated red blood cells. In the presence of a sample containing the antigen for which the antiserum was specific, agglutination was blocked. The sensitivity of this test for IgA and its subgroups was 0.5 to 1.0 mg. per 100 ml.

IgD was also semiquantitatively measured by a hemagglutination-inhibition test, in which sheep red blood cells were coated with IgD myeloma protein (Cro) with the use of glutaraldehyde as described by Evans and co-workers[8] with the minor modification

*Linbro Scientific, Inc., Namden, Connecticut.

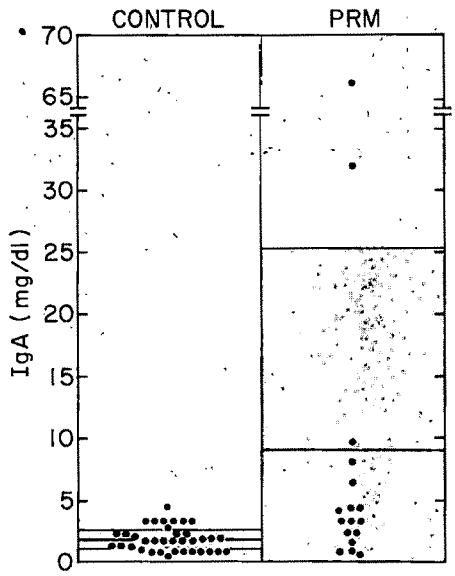


Fig. 1. IgA concentrations milligrams per deciliter in cord blood are shown for 36 normal control samples on the left side of the figure and for 17 samples on the right side of the figure. Each dot denotes a single sample. The mean is shown by a central horizontal bar, and ± 1 standard deviation is shown within the shaded area of the figure.

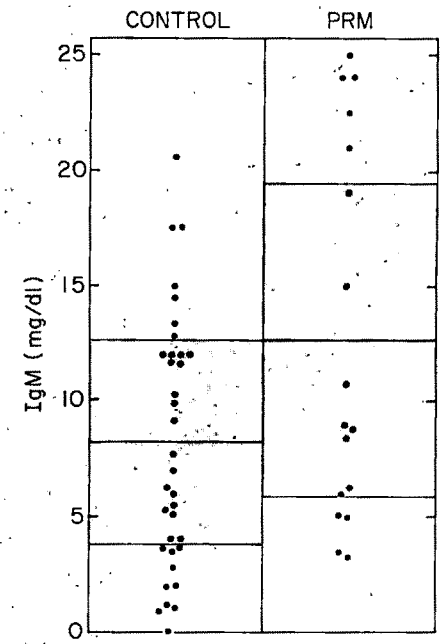


Fig. 2. IgM concentrations milligrams per deciliter in cord blood are shown for 36 normal control samples on the left side of the figure and for 17 samples on the right side of the figure. Each dot denotes a single sample. The mean is shown by a central horizontal bar, and ± 1 standard deviation is shown within the shaded area of the figure.

that Roswell Park Memorial Institute 1640 was substituted for Dubelco medium. R 408 anti-IgD rabbit antiserum was used. Serial dilutions of amniotic fluid and fetal and maternal serum in a 50 μl volume were mixed with 50 μl of antiserum in U-shaped wells of a microtiter plate. After 30 minutes of incubation at room temperature, 50 μl of IgD-coated sheep red blood cells was added to each well. The plate was then left at 4° C. overnight and read along with the IgD standards, myeloma protein Nix. No centrifugation was used in this test, the cells being permitted to settle. In the presence of a sample containing IgD, agglutination was inhibited, and the red cells were seen as a round button in the center of the well. If there was no inhibition, agglutination was observed as a dispersed pattern of cells. The sensitivity of this system was in the range of 0.02 to 0.04 mg. per 100 ml.

IgG and IgM were determined by radial immunodiffusion.[9] Immunodiffusion plates were obtained from a commercial source,* and the samples were read against standard concentrations of immunoglobulins. Precipitation rings were measured after 48 hours for IgA and after 72 hours for IgM. The amniotic fluid samples were concentrated up to 180 times to obtain measurable levels of immunoglobulins. The sensitivity for IgM was 5.4 per 100 ml.; for IgG, 3.6 per 100 ml.

*Kallestad Laboratories Inc., Chaska, Minnesota.

The IgE levels in amniotic fluid and maternal and fetal sera were determined by a radioimmunosorbent technique,[10] the Phadebas IgE test.* An automatic gamma counting system was used.† Levels of IgE as low as 20 ng. per milliliter could be read with confidence.

Results

Comparison of cord blood immunoglobulin concentrations in patients with PRM to the control group demonstrates clear evidence of an immune response occuring in the PRM group (Table I). There was a statistically significant increased level of IgM and a statistically significant decreased level of IgD. IgA values were on an average five times higher in the PRM group than in the control group. Although the difference between groups was not statistically significant for IgA, the wide range of values found in the PRM group suggested that some of the PRM group (but not all) had abnormal elevations of IgA. This was confirmed by plotting the individual values of IgA in Fig. 1. When two standard deviations on either side of the mean of

*Pharmacia AB, Uppsala, Sweden.

†1185 Series, Nuclear-Chicago Corp., 2000 Nuclear Dr., Des Plaines, Illinois 60018.

Table II. Sixteen patients with PRM and their actual concentrations of various immunoglobulins

Sample		*Immunoglobulin*														
		IgA (mg./dl.)			*IgA_1 (mg./dl.)*			*IgA_2 (mg./dl.)*			*IgD (mg./dl.)*			*IgE (ng./ml.)*		
		MS	*CB*	*AF*	*MS*	*CB*	*AF*	*MS*	*CB*	*AF*	*MS*	*CB*	*AF*	*MS*	*CB*	*A*
Ho	(1)	512	2.3		320	2.0		64	0.3		64	0		40	20.0	
Fo	(2)	220	0.8		160	0.8		16	0.01		9.2	0		1,200	21.1	
He	(2)	480	1.5	3.3	256	1.2	3.3	96	0.2	0.6	64	0.1	0.1	166	576	20.
Me	(2)	230	66.1*	7.3	160	51.2*	3.7	16	12.8*	0.2	2.0	0	0	100	43.2	
Se	(2)	357	4.4*	2.0	357	4.5	2.0	32	0.3	0.2	64	0.4	0.1	320	52	7.
Ra	(3)	400	4.4*		320	2.2		64	0.6		1.0	0		300		
El	(6)	256	3.2	6.4	304	2.2	5.7	64	0.3	0.6	2.3	0	0.1	164	56	4.
Si	(6)	320	2.3		320	1.2		13	0.2		4.0	0.5			220	
Br	(14)	102	4.1*		102	2.2		19	0.7		64	0		400	66	
Le	(14)	256	6.4*		240	7.3*		10	0.7		4.6	0.2		240		
Mo	(18)	512			320			64			9.2			86		
Twin A			0.5	3.4		0.4	2.8		0.1	0.3		0.1	0.2			2.
Twin B			0.6	5.6		0.6	3.2		0.1	1.3		0.5	0.1			0
To	(54)	440	8.0*		448	8.0*		8	0.1		9.2	0		152	220	
Sa	(62)	220	3.2		160	3.2		32	0.3		9.2	0		136	33.9	
Ge	(75)	568	3.2		320	3.0		64	0.2		32	0.2		2,600	27.3	
Gr	(315)	1,280	9.6*		960	8.2*		51	0.2		0.1	0		58	10	
De	(648)	256	32*		256	32*		10	0.1		9.2	0		520	76	

The numbers in parentheses are the number of hours of PRM prior to onset of labor. MS, Maternal serum. CB, Cord blood. AF Amniotic fluid. No test was done due to lack of material where no numbers appear.

*Abnormally elevated immunoglobulin values.

the control values are used as the normal range, 47 per cent of patients with PRM had elevated levels of IgA as compared to 3 per cent of the control group.

The elevated levels of IgA in the PRM group were mainly due to an increase in the IgA_1 subgroup, while IgA_2 remained low or increased to a lesser degree (Table II). There was only one exception: Sample Me in Table II had a statistically significant increased level of IgA_2 (12.8 mg. per cent).

Of the 16 patients with PRM, two had elevated IgM and normal IgA values, five had elevated IgA and normal IgM, three had increases in both IgA and IgM, and six had no immunoglobulin abnormalities in cord blood. In the control group, 3 per cent of the subjects had high IgM and 3 per cent had high IgA.

In the present series, there is no evidence that the duration of PRM plays a significant role in the degree of IgA elevation. The highest values in the group were found in the cord blood of a patient with only a two-hour history of PRM, while the lowest values were obtained in a patient with 19 hours of PRM (see Table II). No difference in the length of labor was found between the patients with normal and elevated levels of IgA. Levels of IgM in cord blood also showed no correlation to length of PRM or length of labor (Fig. 2).

The cord blood IgG concentrations in both the group with PRM and the control group are similar (Fig. 3). The IgG levels were not related to the increases in IgA or IgM.

IgD levels in cord blood were significantly decreased in the group with PRM as compared to the control group (Table II and Fig. 4). IgD was detectable in the cord blood of 53 per cent of the patients in the control group and 38 per cent of the patients with PRM. A higher percentage of tested patients had detectable levels of IgD in cord blood than previously reported.[11, 12] IgE was detected in all cord blood samples tested. IgE values were approximately 35 per cent lower in the group with PRM than in the control group; the difference was not statistically significant (Fig. 5).

Among patients with PRM, two had clinical evidence of maternal infection, and labor was induced accordingly with intravenous administration of oxytocin. Mrs. De had a sudden temperature rise to 39° C. and a rise in the white blood cell count from 8.3×10^3 to 15.8×10^3 after 27 days of close observation following PRM. The delivery was normal and resulted in the birth of a 2,210 gram male infant with an Apgar score of 4/8. Blood cultures from maternal serum and cord blood were negative, while a culture from the amniotic fluid obtained at the time of delivery yielded *Streptococcus faecalis*. The mother was successfully treated with ampicillin for endometritis, and the baby had a normal course during his stay in the hospital. Another patient, Gr, had a rise in temperature to 38° C. after a 13 day history of PRM. The white blood cell count had then risen to 15×10^3. Labor was successfully induced, and a 2,700 gram male infant with an Apgar score of 8/10 was delivered. Blood cultures from cord blood and maternal serum were negative. The mother was

IgG (mg./dl.)			IgM (mg./dl.)		
MS	*CB*	*AF*	*MS*	*CB*	*AF*
720	370		124	6.3	
1,430	980		100	6.0	
1,120	361	16	140	3.3	0.03
370	370	12	225	9.0	0.1
640	640	18	200	15.0	0
455	810		215	24.0*	0
1,120	775		225	24.0*	0
1,820	1,150		212	8.8	
1,025	401		23	21.0*	
600	387		240	10.7	
440			170		
	394	11		5.0	0.1
	510	12		5.1	2.0
1,050	370		150	3.5	
910	480		180	19.0	
370	607		225	25.0*	
700	385		120	8.4	
780	280		115	22.5*	

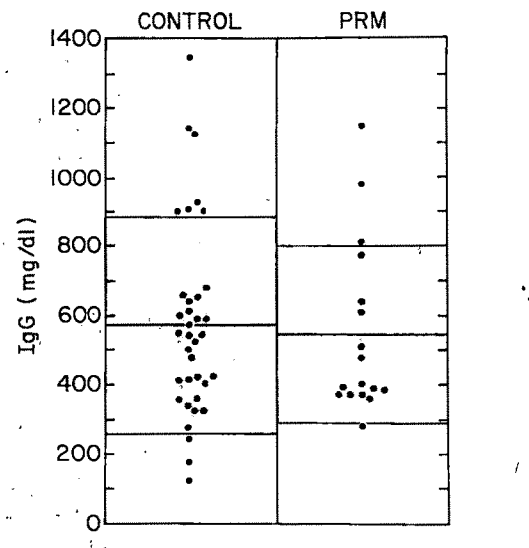


Fig. 3. IgG concentrations milligrams per deciliter in cord blood are shown for 36 normal control samples on the left side of the figure and for 17 samples on the right side of the figure. Each dot denotes a single sample. The mean is shown by a central horizontal bar, and ± 1 standard deviation is shown within the shaded area of the figure.

treated with ampicillin for endometritis, and the mother and child subsequently had a normal course in the hospital.

Only two infants born to mothers with PRM had clinical evidence of infection. Thus, baby girl Le had a temperature exceeding 38° C. the second and third day post partum. Blood culture yielded gram-positive cocci, and she was treated with ampicillin. Another infant, Br, was delivered by cesarean section because of breech presentation with an extended head and developed skin pustules from which *Streptococcus faecalis* was cultured shortly after delivery. Blood culture was negative. The infant was treated with antibiotics and subsequently did well.

All four patients in whom infection was diagnosed in either the mother or the infant had significantly increased levels of IgA in the cord blood; two of these patients (De and Br) also had significantly increased levels of IgM.

Seven patients in the group with PRM has positive bacteriologic cultures from the uterine cavity or the placenta but had no clinical symptoms. Two of the seven had significantly increased levels of IgA and normal amounts of IgM in the cord blood. In one of these cases (Me), peptococci and *Derobie bacillus* were found. In the other case, *Streptococcus viridans* and *Bacterium proprionus* were isolated from the placenta and uterine cavity. Streptococci and *Staphylococcus epidermis* were isolated from the cord blood. A third patient had significantly increased IgM but normal IgA, and streptococci were found on uterine and placental cultures. The remaining four patients (Fo, Ho, Sa, and Se) had normal levels of IgA and IgM. In three of them, cultures from the uterus and placenta yielded *Streptococcus viridans,* while a fourth patient (Sa) had peptococci.

Comment

The results of the present series clearly demonstrate that the fetus develops an immune response in most cases of premature rupture of the membranes followed by amnionitis. There is individual variability in the type of immunoglobulins produced by the fetus when infection occurs: *A significant increase in either or both IgA and IgM or no increase at all may be found.*

The predominance of IgA_1 in the increased level of IgA may be due to either the immune response characteristic of late gestation or a systemic rather than local IgA response.[5] If the increased levels of IgA were produced in early gestation, a high fraction of IgA_2/IgA_1 would be predicted.[5] This would also be expected if local synthesis of IgA occured in the gastrointestinal tract, where the content of IgA_2 is usually close to 50 per cent. Miller and co-workers[13] noted measurable levels of IgA in 5.4 per cent of 5,006 cord blood samples with the use of immunodiffusion plates. These authors interpreted their findings as resulting from a placental leak rather than an immune response. Several of their samples had increased IgA and IgM. There was no information in this paper about PRM.

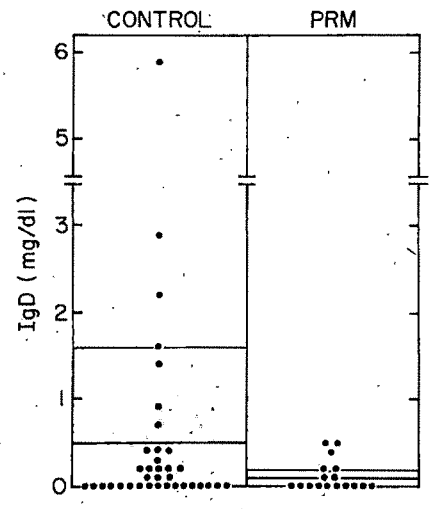


Fig. 4. IgD concentrations milligrams per deciliter in cord blood are shown for 36 normal control samples on the left side of the figure and for 17 samples on the right side of the figure. Each dot denotes a single sample. The mean is shown by a central horizontal bar, and ± 1 standard deviation is shown within the shaded area of the figure.

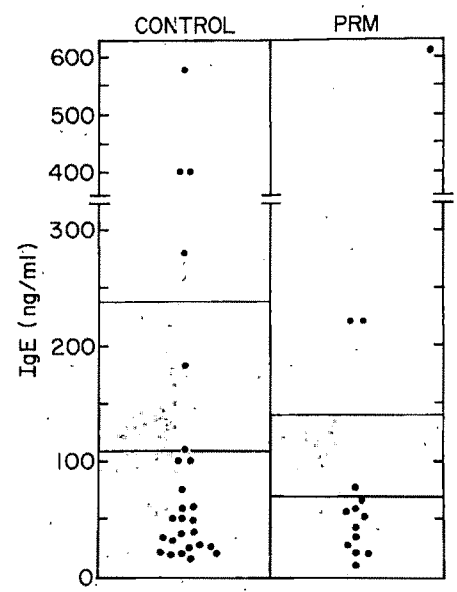


Fig. 5. IgE concentrations nanograms per milliliter in cord blood are shown for 36 normal control samples on the left side of the figure and for 17 samples on the right side of the figure. Each dot denotes a single sample. The mean is shown by a central horizontal bar, and ± 1 standard deviation is shown within the shaded area of the figure.

Demonstration of increased IgM levels in cord blood is now used routinely to diagnose congenital or neonatal infections. It is evident from our results that the presence of PRM with elevated cord blood IgM could result in a false confirmation of a suspected congenital infection. It appears important to determine for the future what intrauterine conditions will provoke a fetal immune response and to include determination of IgA in cord blood in studies, provided a sensitive method is available.

Of considerable interest is the fact that the IgD concentrations are low in the presence of increased levels of IgA or IgM. This correlation could be demonstrated because of the high sensitivity of our method, with which IgD could be detected in cord blood in 53 per cent of the control group and 38 per cent of the PRM group. In contrast, IgD has previously been detected in 4.5 to 8.0 per cent of tested cord blood samples.[11, 12] There is some suggestion of an inverse relationship between elevated IgA and IgM and lowered IgD. It can be calculated from Table II that within the PRM group IgD could be detected in only 25 per cent of the samples in which IgA was elevated and in only 20 per cent of samples in which IgM was elevated; in the three subjects in whom both IgA and IgM were increased, no IgD could be detected in cord blood. The role of IgD during fetal life is unknown, but present data include the suggestion that IgD is found in immature cells. If this is so, an immune response could provoke a switch from IgD synthesis to synthesis of other immunoglobulins within the individual lymphocyte and result in lower cord blood IgD levels. It can be hypothesized that PRM and the resulting antigenic stimulation caused an antigen-driven maturation of the immune response with a fall in the number of IgD-synthesizing lymphocytes in favor of IgA- or IgM-producing cells.

The origin of fetal immunoglobulins is still not totally clear. The similar mean levels of IgG in the PRM and control groups in this study reflect the well-established maternal transfer of IgG through the placenta. Serum IgG has been detected as early as 38 days in a fetus as the result of passive maternal transfer.[14] In amniotic fluid, the IgG is of predominantly maternal origin.[15] In contrast to IgG, IgA, IgD, IgE, and IgM do not pass through the placenta,[16] and thus any Ig other than IgG appearing in cord blood indicates fetal synthesis.

The site of production of IgA in the fetus has not been determined, but recently Petit and co-workers,[17] using immunoelectrophoresis, reported finding secretory IgA in the gut wall and contents of human fetuses from the thirteenth to the twenty-sixth week of gestation. In a previous study from our laboratories, genetic markers were used to demonstrate that IgA_2 found in cord blood and amniotic fluid was of fetal origin.[5]

Determination of immunoglobulin in amniotic fluid has been explored as a means of diagnosing congenital

infection in utero. IgG in amniotic fluid is well documented.[18, 19] By using Gm genetic markers, the majority of the IgG was shown to be of maternal origin.[15] Curl[20] detected IgA in amniotic fluid from 8 of 10 patients at term by radial immunodiffusion, and we have previously reported on the presence of IgA and its subgroups IgA_1 and IgA_2 in amniotic fluid from the fourteenth week of gestation.[5] IgM is usually considered to be absent in amniotic fluid.[20, 21] By concentrating our samples up to 180-fold, IgM was detected in all 27 normal samples tested and in four of seven cases with a history of PRM. IgD previously has not been found in amniotic fluid, but in the present study IgD was detected in 26 of 36 normal samples and in five of six patients with PRM. IgE was found in all 22 normal samples of amniotic fluid tested and in four of five samples in the PRM group.

Future research will aim to clarify the different factors which induce immunologic response in the normally sterile fetal environment and their relationship to production of IgA or IgM or both.

REFERENCES

1. Alford, C. A., Schaefer, J., Blankenship, W. J., Straumfjord, J. V., and Cassady, G.: A correlative immunologic, microbiologic, and clinical approach to the diagnosis of acute and chronic infections in newborn infants, N. Engl. J. Med. **277:** 437, 1967.
2. Stiehm, E. R.: Fetal defense mechanisms, Am. J. Dis. Child. **129:** 438, 1975.
3. Reid, D. E., Ryan, K. J., and Benirschke, K.: *In* Principles and Management of Human Reproduction, Philadelphia, 1972, W. B. Saunders Company, p. 757.
4. Amstey, M. S., and Monif, G. R. G.: Genital herpes virus infection in pregnancy, Obstet. Gynecol. **44:** 394, 1974.
5. Cederqvist, L. L., and Litwin, S. D.: Production of $Alpha_1$ and $Alpha_2$ immunoglobulin heavy chains during fetal life, J. Immunol. **112:** 1605, 1974.
6. Gold, E. R., and Fudenberg, H. H.: Chromic chloride: A coupling reagent for passive hemagglutination reactions, J. Immunol. **99:** 85, 1967.
7. Avrameas, S., Tando, B., and Chuilan, S.: Glutaraldehyde, cyanic chloride and tetrazitized O-dianiside as coupling reagents in the passive hemagglutination tests, Immunochemistry **6:** 67, 1969.
8. Evans, J., Steel, M., and Arthur, E.: A hemagglutination inhibition technique for detection of immunoglobulins in supernatants of human lymphoblastoid cell lines, Cell **3:** 153, 1974.
9. Mancini, G., Carbonara, A. O., and Heremans, J. R.: Immunochemical quantitation of antigens by single radial immunodiffusion, Immunochemistry **2:** 235, 1965.
10. Johansson, S. G. O.: Serum IgND levels in healthy children and adults, Int. Arch. Allergy **34:** 1, 1968.
11. Evans, H. E., Akpata, S. O., and Glass, L.: Serum-Immunoglobulin levels in premature and full-term infants, Am. J. Clin. Pathol. **56:** 416, 1971.
12. Leslie, G. A., and Swate, T. E.: Structure and biologic functions of human IgD. I. The presence of immunoglobulin D in human cord sera, J. Immunol. **109:** 47, 1972.
13. Miller, M. J., Sunshine, P. J., and Remington, J. S.: Quantitation of cord serum IgM and IgA as a screening procedure to detect congenital infection: Results in 5,006 infants, J. Pediatr. **75:** 1287, 1969.
14. Gitlin, D., and Biasucci, A.: Development of gamma G, gamma A, gamma M, beta 1C/beta 1A, C'1 esterase inhibitor, ceruloplasmin, transferrin, hemopexin, haptoglobin, fibrinogen, plasminogen, alpha-1-antitrypsin, orosomucoid, beta-lipoprotein, alpha-2-macroglobulin and pre-albumin in the human conceptus, J. Clin. Invest. **48:** 1433, 1969.
15. Cederqvist, L. L., Queenan, J. T., Gadow, E. C., and Litwin, S. D.: The origin of gamma G globulins in human amniotic fluid, Am. J. Obstet. Gynecol. **113:** 838, 1972.
16. Rowe, D. S., and Fahey, J. L.: A new class of human immunoglobulins. II. Normal serum IgD, J. Exp. Med. **121:** 185, 1965.
17. Petit, J. C., Galinha, A., and Salomon, J. C.: Immunoglobulins in the intestinal content of the human fetus with special reference to IgA, Eur. J. Immunol. **3:** 373, 1973.
18. Monif, G. R. G., and Mendenhall, H. W.: Immunoglobulin G levels and the titers of specific antiviral antibodies in amniotic fluid, Am. J. Obstet. Gynecol. **108:** 651, 1970.
19. Gadow, E. C., Gloriani, F. A., and Florin, A.: IgG levels in amniotic fluid, Am. J. Obstet. Gynecol. **119:** 849, 1974.
20. Curl, C. W.: Immunoglobulin levels in amniotic fluid, Am. J. Obstet. Gynecol. **109:** 408, 1971.
21. Wilfert, C. M., and Alford, C.: No IgM in amniotic fluid, J. Infect. Dis. **129:** 604, 1974.

Intra-amniotic urea and prostaglandin $F_{2\alpha}$ for midtrimester abortion: A modified regimen

RONALD T. BURKMAN, M.D.
MILAGROS F. ATIENZA, M.D.
THEODORE M. KING, M.D., PH.D.
LONNIE S. BURNETT, M.D.
Baltimore, Maryland

A study comparing intra-amniotic urea plus intravenous oxytocin and intra-amniotic urea with 10 mg. prostaglandin $F_{2\alpha}$ was completed. In addition, the results obtained with a further 150 patients receiving urea and prostaglandin are reported. Mean injection-abortion intervals ranged from 15.75 hours for urea-prostaglandin to 18.93 hours for urea-oxytocin. The advantages of urea-prostaglandin and suggested improvements are discussed. Over all, the method appears efficacious though incomplete abortions and cervical laceration are persistent problems.

INVESTIGATORS CONTINUE to search for better methods of inducing midtrimester abortion. Studies by our group and others have demonstrated the efficacy of a single intra-amniotic injection of prostaglandin $F_{2\alpha}$ and hyperosmolar urea without initial intravenous oxytocin augmentation.[1, 2] The use of hyperosmolar urea and prostaglandin E_2 has also been found to be effective.[3–5]

The advantages of intra-amniotic urea and prostaglandin $F_{2\alpha}$ are several-fold. The use of prostaglandin as an augmenting agent appears to impose less concern than oxytocin, particularly in the area of water and electrolyte balance. Also, the need for utilization of the intravenous route is reduced. Thus, this combination of agents can be used in settings when close monitoring of patients for electrolyte and fluid abnormality is not feasible. The metabolic, hematologic, and coagulation changes associated with this method are transient and in general do not appear clinically significant. Finally, mean injection-abortion intervals are less than 24 hours with this technique.

From the Fertility Control Center of the Johns Hopkins Medical Institutions, Department of Gynecology and Obstetrics.

Received for publication October 14, 1975.

Revised February 24, 1976.

Accepted February 24, 1976.

Reprint requests: Roanld T. Burkman, M.D., The Johns Hopkins Hospital, Woman's Clinic, Baltimore, Maryland 21205.

However, there are persisting problems with this method. Failure to abort and incomplete abortions with their need for surgical management continue as problems. The complications of hemorrhage, infection, and cervical laceration have not been eliminated and gastrointestinal side effects during the abortion process persist.

In a prior study, the use of intra-amniotic hyperosmolar urea in conjunction with a 20 mg. dose of prostaglandin $F_{2\alpha}$ was shown to be effective.[1] In the present study the dose of prostaglandin was reduced by half in an attempt to ascertain the minimal effective dose. Intravenous oxytocin was started on unaborted, nonlaboring patients at 24 hours after injection and 4 hours after membrane rupture in an effort to reduce the incidence of prolonged injection-abortion intervals and prevent failure to abort. To evaluate the effectiveness of this modification of our previous regimen, a randomized study was undertaken to compare the results of this technique with those obtained by intra-amniotic urea with oxytocin augmentation, and following this comparative series, an additional 150 cases were completed.

Material and methods

Initially, 60 patients undergoing elective midtrimester abortion were randomly distributed into two treatment groups (Groups R). Thirty received 80 Gm. of urea and 10 mg. of prostaglandin $F_{2\alpha}$ intra-amniotically and 30 received 80 Gm. of intra-amniotic urea with intravenous oxytocin administration at 332

Table I. Clinical characteristics of study groups

	No.	*Mean age*	*Para 0*	*Para 1 or greater*	*Mean duration of gestation (wk)*	*Fluid removed at amniocentesis (c.c.)*
Urea prostaglandin $F_{2\alpha}$, randomized group (R)	30	20.1 (14-32)*	22	8	19.6 (17-24.5)	202.7 (150-300)
Urea-oxytocin, randomized group (R)	30	19.2 (13-29)	20	10	19.2 (15-24)	198.7 (160-290)
Urea-prostaglandin $F_{2\alpha}$, additional study group (S)	150	20.6 (13-41)	74	76	18.9 (16-24)	209.7 (110-425)

*Ranges in parentheses.

Table II. Injection-abortion intervals

	No. cases	*Injection-abortion interval (hr)**			
		Range	*Mean*	*S.E.M.†*	*p value*
Parity: 0					
Urea-$PGF_{2\alpha}$ (R)‡	22	2.67-29.58	16.53	1.78	0.1
Urea-oxytocin (R)	19	9.67-47.67	21.55	2.23	
Urea-$PGF_{2\alpha}$ (S)§	73	2.50-47.33	17.84	1.07	
Parity: 1 or more					
Urea-$PGF_{2\alpha}$ (R)	8	5.83-31.00	13.60	3.63	N.S.
Urea-oxytocin (R)	10	6.92-19.08	13.93	1.22	
Urea-$PGF_{2\alpha}$ (S)	76	6.00-48.33	15.12	1.14	
Total groups:					
Urea-$PGF_{2\alpha}$ (R)	30	2.67-31.00	15.75	1.61	N.S.
Urea-oxytocin (R)	29	6.92-47.67	18.93	1.65	
Urea-$PGF_{2\alpha}$ (S)	149	2.50-48.33	16.45		

*From intra-amniotic injection of medication to abortion of fetus.
†Standard error of the mean.
‡(R)-randomized groups.
§(S)-additional study group.

mU. per minute. With completion of the comparative series, an additional 150 consenting patients received 80 Gm. of urea and 10 mg. of prostaglandin $F_{2\alpha}$ (Group S).

Our methods of preoperative patient evaluation, basic techniques of abortifacient administration, and methods of intra- and postabortal management of patients were not altered from our previous study except as noted below.[1] The definitions for incomplete abortion and failed procedures also remained the same. If, after approximately 48 hours following the injection of intra-amniotic urea, the patient was not in labor and/or abortion of the fetus was not thought to be imminent, the procedure was considered to be a failure. Incomplete abortion was defined as failure to expel the placenta spontaneously within 2 hours following passage of the fetus. Such patients underwent "sponge-stick" curettage. Similarly, if fever or excessive bleeding occurred prior to the imposed 2 hour limit, curettage was undertaken sooner and the patients were reported as having incomplete abortions.

All patients receiving oxytocin had serum electrolytes evaluated at 12 hours after initiation. No other laboratory data were routinely collected in this study.

Patients receiving urea-prostaglandin had 7.5 mg. of prostaglandin $F_{2\alpha}$ administered intra-amniotically 5 minutes after a 2.5 mg. test dose, to give a total dosage of 10 mg. Also, at 24 hours postinjection or at 4 hours following spontaneous rupture of membranes, if unaborted and if not felt to be in labor following examination by one of the investigators, patients receiving urea-prostaglandin were started on intravenous oxytocin at 332 mμ per minute. The above constitute the only changes from our previous protocol.[1]

During the study, the following data were collected: age, parity, gestational age, fluid removed at amniocentesis, injection-abortion interval, complete versus incomplete abortion, gastrointestinal side effects, body weight change, and all complications.

The means and standard error of the means were calculated for injection-abortion intervals, age, duration of gestation, fluid removed at amniocentesis, and

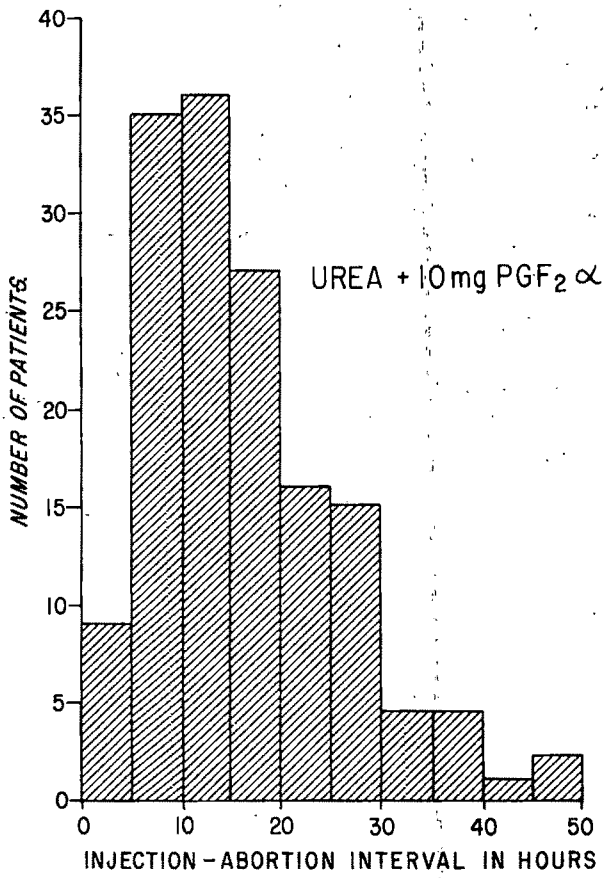


Fig. 1. Distribution of injection-abortion intervals by 5 hour time periods for 149 patients receiving intra-amniotic urea and 10 mg. of prostaglandin $F_{2\alpha}$. One patient failed to abort.

body weight change. These data were then analyzed by an F test and Student's t test in order to determine statistical significance.

Results

Clinical characteristics of the groups. Table I details the clinical characteristics of the three groups of patients. There was no significant difference in any of the parameters among the groups with the exception of an increased proportion of multiparous patients in the urea-prostaglandin additional study group.

Injection-abortion intervals. Table II details the injection-abortion intervals. Although differences between groups were noted, only the difference between the nulliparous urea-prostaglandin and urea-oxytocin randomized groups was significant.

Fig. 1 displays the number of patients aborted within 5 hour time periods for the urea-prostaglandin additional study group. The cumulative abortion rates at 12, 24, 36, and 48 hours for the para 0 versus para 1 or greater patients respectively in this additional study group were: 24.7 and 44.7 per cent; 78.1 and 77.6 per cent, 94.5 and 94.7 per cent; and 100 and 100 per cent.

Outcome. Table III details the outcome of patients in all groups. There were no failed procedures in the urea-prostaglandin randomized group but one failed procedure occurred in both the urea-oxytocin randomized and urea-prostaglandin additional study groups. Curettage with local anesthesia and intravenous analgesia was utilized to manage both the incomplete abortions and the procedure failures. At no time was general anesthesia used in this study.

Intravenous infusions in the urea-prostaglandin groups. In the randomized and additional study groups, 55.1 and 76.0 per cent of the patients had intravenous infusions, respectively. A detailed analysis of the additional study group revealed the following indications. Of the 111 patients receiving intravenous infusions, 23.4 per cent had inadequate oral intake of fluids, 19.8 per cent had failed to abort by 24 hours, 42.3 per cent received oxytocin 4 hours following ruptured membranes, and 33.4 per cent received oxytocin for retained placenta or postabortal bleeding.

Body weight. The mean body weight change in the urea-prostaglandin randomized group was a loss of 4.38 pounds (range 1 to 11.3 pounds) while in the urea-oxytocin randomized group the mean weight decrease was 3.99 pounds (range 0 to 7.5 pounds). There was no statistical difference between the two groups.

Immediate complications (Table IV).

1. Failure of the primary procedure. There was one failed procedure in the randomized urea-oxytocin group and one in the urea-prostaglandin additional study group. Both patients had failed to abort at 48 hours and were managed by vaginal evacuation via "sponge-stick" curettage under local anesthesia.

2. Hemorrhage. In the urea-prostaglandin randomized group, the estimated blood loss ranged from 75 to 900 c.c. with a mean of 257 c.c., in the urea-oxytocin randomized group the range was from 25 to 500 c.c. with a mean of 217 c.c., while in the urea-prostaglandin additional study group the range was 35 to 1,500 c.c. with a mean of 212 c.c. There was no significant difference among the groups, and no patients required transfusions.

Only one patient in the urea-oxytocin randomized group, the failed procedure, had a blood loss exceeding 500 c.c. Of the four patients with greater than 500 c.c. blood loss in the urea-prostaglandin randomized group, three underwent "sponge-stick" curettage for placental removal. Similarly, in the urea-prostaglandin additional study group, eight of the 10 patients with bleeding in excess of 500 c.c. also underwent curettage for placental removal.

3. Infection. No patients in the randomized groups required treatment for infection developing prior to or immediately after abortion. Three patients in the urea-prostaglandin additional study group had their admission prolonged due to infection. Two patients were diagnosed as having probable chorioamnionitis during the abortion process, aborted without instrumentation, and received curettage and parenteral antibiotics. One patient was treated for acute tonsillitis evident postabortal. All three patients did well.

4. Untoward gastrointestinal effects. Seventy per cent of patients in the randomized urea-prostaglandin group, 60 per cent of patients in the randomized urea-oxytocin group, and 70 per cent in the urea-prostaglandin additional study group experienced emesis. The mean number of episodes was 3.95 (range 1 to 15) and 2.11 (range 1 to 4) in the urea-prostaglandin and urea-oxytocin randomized groups, respectively, and 2.99 (range 1 to 7) in the additional study group. The difference was significant ($p < 0.05$) between the two randomized groups. No patient in either randomized group experienced diarrhea, although two patients in the additional study group had one episode each.

5. Inadvertent intravascular injection. One patient in the urea-oxytocin group had an intravascular injection or spill of hyperosmolar urea. This 21-year-old, para 0 patient was estimated to be 17 weeks pregnant. At amniocentesis, 160 c.c. of slightly bloody fluid was removed. Immediately following the urea injection, the patient complained of a severe headache. A serum urea nitrogen done within 30 minutes of the injection revealed a value of 93 mg. per 100 ml. Intravenous oxytocin was not begun in order to allow osmotic diuresis to occur without the antidiuretic effect of oxytocin. At 16 hours after injection, the serum urea nitrogen was within normal limits and intravenous oxytocin was then initiated with abortion occurring within 1 hour. The patient was discharged asymptomatic several hours later.

6. Cervical laceration. No cervical lacerations were noted in either randomized group, but a total of six were detected in the urea-prostaglandin additional study group. Four lacerations were vertical and located posteriorly. Three were less than 2 cm. long, while the other was about 5 cm. in length. Among the six cervical lacerations, only the 5 cm. vertical laceration extended to or beyond the internal os. All vertical lacerations were immediately repaired except for one 1 cm. tear, and all showed good healing at follow-up with the exception of the 5 cm. laceration. This laceration was noted to be broken down 3 days after abortion, when the patient was readmitted with endometritis. At subsequent follow-up, some healing had occurred though a significant amount of scarring remained.

Table III. Outcome

	No. of Cases	Complete abortion		Incomplete abortion		Failure	
		No.	%	No.	%	No.	%
Parity: 0							
Urea-$PGF_{2\alpha}$ (R)*	22	16	72.8	6	17.2	0	
Urea-oxytocin (R)	20	13	65.0	6	30.0	1	5.0
Urea-$PGF_{2\alpha}$ (S)†	74	40	54.0	33	44.6	1	1.4
Parity: 1 or more							
Urea-$PGF_{2\alpha}$ (R)	8	3	37.5	5	62.5	0	
Urea-oxytocin (R)	10	7	70.0	3	30.0	0	
Urea-$PGF_{2\alpha}$ (S)	76	39	51.4	37	48.6	0	
Total:							
Urea-$PGF_{2\alpha}$ (R)	30	19	63.3	11	36.7	0	
Urea-oxytocin (R)	30	20	66.7	9	30.0	1	3.3
Urea-$PGF_{2\alpha}$ (S)	150	79	52.6	70	46.7	1	0.7

*(R)-randomized groups.
†(S)-additional study group.

Table IV. Complications

	Urea-prostaglandin $F_{2\alpha}$ (R) (30 cases)	Urea-oxytocin (R) (30 cases)	Urea-prostaglandin $F_{2\alpha}$ (S) (150 cases)
Immediate			
Failed primary procedure	0	1	1
Hemorrhage greater than 500 c.c.	4	1	10
Infection	0	0	3
Emesis	21	18	105
Inadvertent intravascular injection of urea	0	1	0
Cervical laceration	0	0	6
Delayed			
Re-admitted secondary to infection	0	2	2
Re-admitted for curettage due to bleeding	0	0	2
Infection treated as an outpatient	1	2	6
Bleeding treated as an outpatient	0	0	5

Two lacerations were transverse posterior cervical tears of 3 to 4 cm. in length. One was immediately repaired in two layers with interrupted catgut suture with a good anatomic result by the time of follow-up. Despite routine speculum and postabortion digital cervical-vaginal examination, one transverse laceration was not detected until the 1 month follow-up.

Delayed complications (Table IV).

1. Re-admissions. Two patients in the randomized urea-oxytocin group and two in the urea-prostaglandin

additional study group were readmitted for endometritis. All patients responded within 5 days to parenteral antibiotics and curettage.

Two patients in the urea-prostaglandin additional study group were readmitted as outpatients for curettage with the diagnosis of incomplete abortion. A moderate amount of tissue was obtained in each instance and both were sent home without further problems. No patients in the randomized urea-prostaglandin group required readmission.

2. Outpatient problems. One patient in the randomized urea-prostaglandin group, two patients in the randomized urea-oxytocin group, and six patients in the urea-prostaglandin additional study group were treated with oral antibiotics for endometritis.

In the urea-prostaglandin additional study group, five patients received oral methylergonovine maleate for persistent bleeding diagnosed as possible subinvolution, one patient received analgesics for abdominal cramping, and one patient was seen due to breast engorgement.

3. Miscellaneous problems. Of interest are some of the additional problems noted in all groups either at initial evaluation or during the time of study. Six patients were diagnosed and treated for cervical gonorrhea and two patients were treated for syphilis. One patient was noted to have a cervical band or synechia which required division at the time of abortion. Two patients had persistent abnormal Pap smears. Concurrent medical-surgical problems encountered included lupus erythematosus, epilepsy, heroin addiction, congenital and rheumatic heart disease, and large uterine myomas. Such findings stress the need for careful preoperative evaluation of all elective abortion patients.

Comment

This study demonstrates that about 80 per cent of patients will achieve injection-abortion intervals of less than 24 hours utilizing a 10 mg. dose of prostaglandin $F_{2\alpha}$ in conjunction with hyperosmolar urea. The study also shows that about 40 per cent of multiparous patients abort within 12 hours, but that differences between parous and nulliparous patients are no longer evident by 24 hours and beyond.

Although failed primary procedures are not a major problem, incomplete abortions continue to require surgical management. The imposed 2 hour time limit for retained placenta in this study may account for some of the incompletes, but others also report rates of incomplete abortion ranging from 20 to 60 per cent.[2, 4, 5] One explanation may be that the prolonged, sustained myometrial contractility achieved with this method may lead to placental entrapment or uterine refractoriness to oxytocic agents after passage of the fetus. Future studies will be directed towards either withholding oxytocic agents or decreasing their dosage in an attempt to reduce this problem.

Utilizing this protocol, a large proportion of urea-prostaglandin patients still require intravenous infusion with more than 70 per cent receiving oxytocin. Since about 80 per cent of patients abort by 24 hours, the time of infusion is usually far less than with urea-oxytocin, thus reducing the potential risk for fluid and electrolyte imbalance.

The complications of infection, hemorrhage, and emesis are certainly not untoward with this method. The sequelae of inadvertent intravascular injection of urea may be self-limiting, especially if oxytocin is withheld. Thus, risk associated with such spill of hyperosmolar urea appears far less than with hypertonic saline.

The 4 per cent rate of cervical laceration in the urea-prostaglandin additional study group is certainly of some concern. Five of the six lacerations occurred in nulliparous patients and two-thirds were vertical. Craft also experienced a 4.5 per cent cervical laceration rate with all tears being vertical in location.[5] These findings mandate careful routine speculum and digital exploration of the lower genital tract after midtrimester abortion, since in this series, despite routine examination, one case went undetected until follow-up. Others have suggested an association with shortened injection-abortion intervals, the use of oxytocic agents, and nulliparity[6] and that such lacerations can occur even with the use of laminara tents.[7] Unfortunately, many reported series detailing varying methodologies for midtrimester abortion have not included routine cervical inspection in their protocols, such that comparative rates for cervical laceration are unavailable. Another problem is the lack of consistent terminology. Cervical lacerations associated with midtrimester induced abortions follow a rupture or tear in the cervix usually due to lack of adequate dilatation and effacement during the abortion process. Others have termed this event a cervical rupture. If such lacerations are not successfully repaired and a communication persists between the cervical canal and vagina, the terms cervical fistula or cervicovaginal fistula are often used.

Immediate repair with interrupted catgut suture in two or more layers following debridement may be the surgical treatment of choice, yet despite such repair, breakdowns frequently occur. Whether prophylactic antibiotics or a change in technique would improve initial results is unknown at this time. Once breakdown has occurred, optimal further management is unclear

since re-repair is associated with a high incidence of surgical failure.[6] At least one case of delivery of a term infant through an unrepaired transverse laceration or cervicovaginal fistula has been reported.[8]

Of obvious concern also is the behavior of such scars in future pregnancies even with successful repair. In addition to careful follow-up, the use of cervical cerclage operations or even delivery via cesarean section may be appropriate in such individuals. Furthermore, whether the ability to become pregnant is seriously impaired also requires careful study. Perhaps further reduction in prostaglandin $F_{2\alpha}$ dosage will make the procedure more like a physiologic process and decrease the rate of cervical laceration.

REFERENCES

1. King, T. M., Atienza, M. F., Burkman, R. T., Burnett, L. S., and Bell, W. R.: The synergistic activity of intra-amniotic prostaglandin $F_{2\alpha}$ and urea in the midtrimester elective abortion, AM. J. OBSTET. GYNECOL. **120:** 704, 1974.
2. Craft, I. L., Walker, E., and Youssefnejadian, F.: Intra-amniotic prostaglandin $F_{2\alpha}$ and urea for abortion, Prostaglandins **5:** 397, 1974.
3. Craft, I. L.: Intra-amniotic prostaglandin E_2 and urea for abortion, Lancet **1:** 1344, 1973.
4. Bowen-Simpkins, P.: The induction of second trimester abortions using an intra-amniotic injection of urea and prostaglandin E_2, J. Obstet. Gynaecol. Br. Commonw. **80:** 824, 1973.
5. Craft, I. L.: Intra-amniotic urea and low-dose prostaglandin E_2 for midtrimester termination, Lancet **1:** 1115, 1975.
6. Goodlin, R., Newell, J., O'Hare, J., and Sturz, H.: Cervical fistula. A complication of midtrimester abortion, Obstet. Gynecol. **40:** 82, 1972.
7. Lischke, J. H., and Gordon, H. R.: Cervico-vaginal fistula complicating induced midtrimester abortion despite laminaria tent insertion, AM. J. OBSTET. GYNECOL. **120:** 852, 1974.
8. Pelosi, M. A., Langer, L., Harrigan, J. T., Devaneson, M., and Zanvettor, J.: Term delivery through a cervico-vaginal fistula, AM. J. OBSTET. GYNECOL. **122:** 789, 1975.

Symposium on Perinatal Medicine

Clinical and biochemical aspects of perinatal medicine will be the subject of a two-day symposium at Christ Hospital in Oak Lawn, Illinois, on October 25 and 26, 1976. Guest lecturers include nationally and internationally known figures in perinatal medicine.

Additional information may be obtained from Dr. M. Rathi or Dr. S. Kumar, Christ Hospital, 4440 W. 95th St., Oak Lawn, Illinois 60453. Telephone: (312) 425-8000, Ext. 5690.

Spontaneous rupture of the liver in pregnancy: A report of eight cases

LESTER T. HIBBARD, M.D.

Los Angeles, California

Seven cases of ruptured subcapsular hematoma and one case of ruptured hepatoma are reported. Six of the patients died, four following an unsuccessful operation. One patient survived following an operation, and another patient survived without surgical intervention. Both survivors were treated with a gravity suit to control internal hemorrhage.

SPONTANEOUS RUPTURE of the liver in the absence of a history or evidence of external trauma is a rare and catastrophic complication of pregnancy. As described in numerous case reports,[1-7] the typical course of events is formation of a large subcapsular hematoma in the right hepatic lobe with secondary rupture of Glisson's capsule to produce a massive intra-abdominal hemorrhage. Although maternal death is likely, approximately 30 per cent of those patients treated by prompt surgical intervention have survived.[8] Sometimes the liver will contain a specific lesion to account for hemorrhage, but more commonly there will be only a variable amount of necrosis of uncertain etiology.

The following is a report of eight additional cases of spontaneous hepatic rupture that resulted in six maternal and eight fetal deaths (Table I).* In six of these cases there was a large subcapsular hematoma with rupture of the liver capsule as proved by laparotomy or autopsy. The seventh patient presumably had a hematoma, the diagnosis having been supported by a celiac angiogram that clearly demonstrated a large avascular area in the right hepatic lobe and by the discovery of a hemoperitoneum at the time of peritoneal dialysis. The eighth patient had a ruptured benign hepatoma. Seven women underwent laparotomy with one surviving, and one case was successfully managed by intensive medical care. A unique feature in the management of the two survivors was the use of an antigravity suit to control internal hemorrhage.

From the Los Angeles County–University of Southern California Medical Center and the Maternal Mortality Committee of the Los Angeles County Medical Association.

Received for publication December 18, 1975.

Revised February 6, 1976.

Accepted February 24, 1976.

Reprint requests: Dr. Lester T. Hibbard, Women's Hospital, 1240 N. Mission Rd., Los Angeles, California 90033.

**These cases were encountered during a 16 year period between 1960 and 1975. The six deaths are from the files of the Maternal Mortality Committee of Los Angeles County–University of Southern California Medical Center. During this period, there were approximately 1,800,000 reportable births in Los Angeles County. Seven of the eight patients had a large subcapsular hematoma with capsular rupture, and the eighth patient had a ruptured hepatoma. None of the patients gave any history or exhibited any evidence of antecedent trauma as being the cause of rupture.*

Case reports

Case 1. A 30-year-old black woman, para 3, was admitted to a hospital in the twenty-third week of pregnancy with a history of ruptured membranes for the past two days. Three preceding pregnancies had been complicated, one by toxemia, one by a pleural effusion, two by unexplained stillbirths, and all three by persisting glycosuria.

On admission, the clinical picture was consistent with a septic inevitable late abortion. There was a thick foul cervical discharge containing gram-negative bacilli, associated with a temperature of 101.4° F., pulse of 102 beats per minute, and a white blood cell count of 18,000 per cubic millimeter. Treatment included an infusion containing 2.0 Gm. of chloramphenicol and 1 Gm. of hydrocortisone followed by an infusion of oxytocin. A 400 gram stillborn fetus was aborted.

Fourteen hours later, the patient complained of epigastric pain. Soon there was hypotension and oliguria associated with a rise of central venous pressure to 130 mm. of water. A bilateral midabdominal paracentesis returned free blood.

An operation was begun with a blood pressure of 0/0 mm. Hg and blood running through three infusion lines. There was a 3,000 ml. hemoperitoneum from 2½ inch long and 1½ inch deep laceration in a subcapsular

Table I. Spontaneous rupture of the liver

Case No.	*Age of patient*	*Parity*	*Duration of pregnancy*	*Operation*	*Outcome*		*Contributory factors*
					Maternal	*Fetal*	
1	30	3	23 wk.	Laparotomy	Died	Stillborn	Diabetes (?)
2	44	11	25 wk.	Repair and cesarean section	Survived	Stillborn	Diabetes (?), hypertension
3	27	2	30 wk.	1. Repair 2. Resection	Died	Stillborn	Hypertension
4	34	1	35 wk.	—	Died	Undelivered	Hypertension
5	34	2	38 wk.	Resection	Died	Stillborn	Fatty metamorphosis
6	34	8	Term	—	Died	Undelivered	Benign hepatoma
7	34	4	Term	Laparotomy	Died	Stillborn	Toxemia, diabetes
8	29	1	Term	—	Survived	Stillborn	Toxemia

hematoma beneath the dome of the right hepatic lobe. By the time the laceration was located and exposed, the patient suffered an irreversible cardiac arrest. During the course of the surgical procedure, 7,000 ml. of blood was replaced.

An autopsy did not furnish any additional explanation of the cause of the laceration.

Case 2. A 44-year-old woman, para 11, in the twenty-fifth week of a previously uneventful pregnancy, was admitted to a hospital with a one-hour history of severe epigastric pain. There was a past history of moderate hypertension and an abnormal glucose tolerance curve during the last pregnancy. The pertinent findings were blood pressure, 150/100 mm. Hg; pulse, 100 beats per minute; temperature, 98° F.; a tense, tender abdomen which did not permit palpation of the uterine fundus; normal fetal heart rate; and a hematocrit of 40 per cent.

In the next 20 hours, the patient complained of increasing abdominal pain and pain referred to the right shoulder. When the hematocrit dropped to 31 per cent, a surgical consultant advised an exploratory laparotomy for a presumptive diagnosis of hemoperitoneum. At operation, there was a hugh subcapsular hematoma of the liver dome which had ruptured along its margins, releasing 2,000 ml. of free blood. A stillborn infant was delivered by cesarean section; the hematoma was evacuated, and the liver was closed with multiple mattress sutures.

During the next 18 hours, the patient was kept in a gravity suit where her condition remained stable. Recovery was uneventful except for continuing hypertension. Subsequent liver function tests were normal.

A liver biopsy taken at the time of operation showed focal necrosis and hemorrhage. Total blood replacement was 5,000 ml.

Case 3. A 30-year-old white woman, para 2, abortion 1, in the thirtieth week of pregnancy, was admitted to a hospital with a four-day history of right upper-quadrant pain. On the morning of admission, she had vomited once and for the first time noted pedal edema.

The past history was not significant except for minimal hypertension for six years which had not required medications. During pregnancy, the blood pressure on eight occasions had ranged from 110 to 120 mm. Hg systolic and 70 to 80 mm. Hg diastolic. There had been no albuminuria and no unusual weight gain, and a recent hemoglobin level was 13.3 Gm.

On admission, the blood pressure was 170/120 mm. Hg, as compared to a reading of 120/80 mm. Hg obtained three days previously. There was nonpitting ankle edema and no albuminuria. The hemoglobin was 12.0 Gm. with a white blood cell count of 8,400 per cubic millimeter with 75 per cent polymorphonuclear leukocytes and 3 per cent bands. Abdominal findings were unremarkable except for right upper-quadrant tenderness not associated with uterine spasm or evidence of fetal distress. Treatment consisted of ½ grain of intramuscular phenobarbital and 10 mg. of diazepam.

On the following evening, the right upper-quadrant pain increased, and there was radiation of pain to the right shoulder. In the next two hours, there was shock associated with generalized abdominal pain and a falling hematocrit. At operation, the findings were 1,100 ml. of free intraperitoneal blood, a large subcapsular hematoma in the dome of the right lobe of the liver, and a one-inch surface laceration. The laceration was repaired, and 1,500 ml. of blood was given. Nine hours later, a second operation was done because of continued bleeding from an incisional drain which had required an additional 10 U. of blood. A 3½ pound stillborn infant was delivered, and a right hepatic lobectomy was attempted because of continued bleeding from the massive subcapsular hematoma. The patient died during the operation following a third episode of cardiac arrest. A total of 24 U. of blood had been given. An autopsy did not provide a further explanation of the cause of rupture.

Case 4. A 27-year-old black woman, para 1, in the thirty-fifth week of pregnancy, had a two-day history of sharp, constant epigastric pain which was increased with deep inspiration. The past medical history was noncontributory, and the present pregnancy was un-

eventful except for mildly elevated blood pressure; ten readings ranged from 118 to 136 mm. Hg systolic and 78 to 90 mm. Hg diastolic. There had been no albuminuria.

The patient was examined twice, with a first impression of dyspepsia and a second impression of probable anxiety. There were no abnormal findings noted except for a pulse of 100 beats per minute on both occasions. The pain persisted for the next five days, at which time the patient was admitted to a hospital for observation.

On admission, the significant physical findings were: blood pressure, 154/94 mm. Hg; pulse, 96 beats per minute; respirations, 32 per minute; and epigastric tenderness that did not seem to involve the uterus. Laboratory findings were: hemoglobin, 11.5 Gm, white blood cell count, 7,000 per cubic millimeter with 81 per cent polymorphonuclear leukocytes; negative urinalysis; and amylase less than 320. A peritoneal tap by a surgical consultant was unproductive. No diagnosis was made except for possible early labor.

A nasogastric tube was passed with some relief of pain. Twelve hours later, there was increasing abdominal pain associated with a pulse of 128 beats per minute and a blood pressure drop to 80/40 mm. Hg. In the next hour, there was evidence of profound shock ending in a cardiac arrest that did not respond to external massage.

Autopsy findings were meticentric subcapsular and parenchymal hemorrhage of the right and left lobes of the liver associated with spontaneous rupture of a huge subcapsular hematoma of the right lobe and a hemoperitoneum of 1,500 ml. An unborn fetus weighed 3,250 grams.

Case 5. A 32-year-old Oriental woman, para 2, was admitted to a hospital in the thirty-eighth week of pregnancy complaining of constant upper abdominal pain of a few hours' duration. The past history was unremarkable, and the prenatal course was uneventful.

On admission, the findings included: blood pressure, 130/100 mm. Hg; hemoglobin, 11.1 per cent with a white blood cell count of 12,800 per cubic millimeter and 73 per cent polymorphonuclear leukocytes. The urine was negative for albumin, and no abnormal abdominal findings were described. Immediate treatment consisted of 50 mg. of meperidine, 25 mg. of promethazine, and an intervenous infusion of dextrose containing 500 mg. of tetracycline.

Eight hours later, abdominal rigidity was noted, and shortly thereafter there was evidence of shock. At operation, a massive hemoperitoneum was encountered. After extraction of a depressed 2,200 gram infant, an exploration of the upper abdomen disclosed a large subcapsular hematoma involving the right hepatic lobe with a six-inch laceration on the liver dome. An attempt at hemostasis included resection of a portion of the liver and multiple sutures. Despite the administration of 3,500 ml. of blood, an irreversible cardiac arrest occured during abdominal closure. The resected liver parenchyma, weighing 510 grams, and exhibiting a yellow-brown color, was reported as showing evidence of fatty metamorphosis.

Case 6. A 34-year-old white woman, para 8, was admitted to a hospital at term with a history of upper abdominal and chest pain, nausea, air hunger, and leaking membranes. One year previously, she had been found to have hepatomegaly which seemed to disappear after oral contraceptives were discontinued. Liver function tests were said to have been normal.

On admission, she was moribund with a blood pressure which initially was 0/0 mm. Hg and rose momentarily to 68/0 mm. Hg with the institution of shock therapy. One hour after admission, she was dead despite vigorous resuscitative efforts.

Autopsy findings were a ruptured benign hepatoma which had occupied one third of the right hepatic lobe, massive hemoperitoneum, and a grossly normal unborn term infant. The possibility that oral contraceptives can be cause of a hepatoma has been the subject of a number of reports.[9]

Case 7. A 34-year-old white woman, para 4, was admitted to a hospital at term complaining of severe right upper-quadrant abdominal pain for the past several hours. She had no prenatal care but was known to have had an abnormal glucose tolerance curve for the past two years.

On admission, the pertinent findings were: blood pressure, 194/120 mm. Hg; 3+ albuminuria; marked deep upper abdominal tenderness not related to a soft relaxed uterus; and no fetal heart tones. The provisional diagnosis was gastritis or cholecystitis associated with toxemia and fetal death.

Three hours later, while under observation in a labor room and during an intravenous infusion, the patient went into shock. Upper abodominal paracentesis returned free blood. Shock measures were instituted; unmatched blood was given, and an operation was begun despite the fact that no blood pressure could be obtained. The abdominal cavity contained 2,000 ml. of free blood originating from a large subcapsular hematoma of the right hepatic lobe, with a bleeding laceration. After 30 minutes of operation and administration of 3,500 ml. of blood, the patient suffered an irreversible cardiac arrest. The stillborn infant weighed 14 pounds. A random maternal blood sugar measurement was 756 mg. per cent.

Liver biopsy taken at the time of operation showed multifocal hemorrhagic hepatic necrosis with some regenerative reaction. Autopsy was refused.

Case 8. A 29-year-old white woman, para 1, was observed in a hospital during the thirty-sixth week of pregnancy in false labor. Despite a resting blood pressure of 158/94 mm. Hg and 2+ albuminuria, the

possibility of pre-eclampsia was ignored. At 40 weeks, she was readmitted with a blood pressure of 250/150 mm. Hg, 2+ albuminuria, and complaining of right upper-quadrant pain. Initial therapy included 20 mg. of hydralazine, 0.5 mg. of reserpine, and 80 mg. of furosemide. Shortly thereafter, she was delivered of a stillborn term infant, and the blood pressure fell to 94/60 mm. Hg.

In the next 24 hours, the hemoglobin dropped from 10.3 to 6.9 per cent. A celiac angiogram showed an avascular area in the right lobe of the liver surrounded by stretched vessels and consistent with a diagnosis of hematoma.[10] Supporting therapy included 1,000 ml. of packed cells, cryoprecipitate, fresh frozen plasma, and three platelet packs.

On the following day, she was transferred to a second hospital with a respirator and with a central venous catheter in place. On admission, she was obtunded and distended. An initial hemoglobin was 9.9 Gm. with a hematocrit of 29 per cent and a platelet count of 75,000 per cubic millimeter. There was no other evidence of disseminated intravascular coagulation. Respiratory arrest occurred when she was temporarily taken off the respirator.

In the ensuing week, "shock lung" complicated by hyponatremia and hyperkalemia was successfully treated by a volume respirator, and oliguric renal failure was counteracted by peritoneal dialysis (blood urea nitrogen 170 and creatinine 8.5). With the institution of peritoneal dialysis, a hemoperitoneum was encountered, but the return fluid, which had an initial hematocrit of 38 per cent, cleared. Subsequently, hemodialysis was substituted for peritoneal dialysis because surgical consultants feared that the dialysis fluid would lyse hemostatic clots. On the third day of hospitalization, the patient's hematocrit dropped from 41 to 27 per cent, and she was treated with a gravity suit in the hope of controlling suspected continuing internal hemorrhage. Additional blood products had included 2,500 ml. of whole blood, 1 U. of packed cells, 10 U. of platelets, and 3 U. of fresh frozen plasma.

From this point, the patient's condition stabilized, and there was a gradual return of renal and hepatic function.

Comment

While hepatic rupture is sometimes due to a specific lesion such as a tumor or an abscess, in the majority of cases it is preceded by the formation of a subcapsular hematoma of uncertain etiology. Among the factors that might contribute to hepatic necrosis and hematoma formation, the most likely appear to be vascular diseases (particularly toxemia) and disseminated intravascular coagulation. Three of the patients in this series has chronic hypertensive disease, and two had toxemia. In addition, one patient was known to have diabetes, and two others had clinical evidence suggesting latent diabetes. As previously mentioned, one patient had a hepatoma and a second had liver changes consistent with a diagnosis of fatty metamorphosis.*

The typical patient with spontaneous rupture of the uterus is described as being older, multiparous, in the third trimester of pregnancy, and having a presenting complaint of upper abdominal pain. The patients in this report fit that description, having an average age of 33, a parity of 4, a gestation of 34 weeks, and abdominal pain centered in either the epigastrium or the right upper quadrant. But in seven of the eight cases, a diagnosis of ruptured viscus was considered only following the onset of a clinical picture of shock. In three cases, the presence of hemoperitoneum was verified by paracentesis which yeilded nonclotting blood. A fourth patient had a negative paracentesis, possibly because the procedure was performed prior to rupture of a subcapsular hematoma.

Although six of the eight mothers died, only one reached the hospital too late to benefit from definitive therapy. Another patient went into irreversible shock while under observation. Only one of the five patients treated by surgical intervention survived. The common surgical problem responsible for all four deaths was inadequate surgical hemostasis at the site of injury. Three of these patients died primarily as a result of hypovolemic shock during the course of operation, and the fourth died during a second operation done because of continuing hemorrhage following initial attempts at hemostasis.

The one patient surviving without surgical intervention illustrates the efficacy of many of the supportive measures now available for critically ill patients. After an initial opportunity to intervene surgically had been lost, the patient's respiratory problem became so severe that an operation was contraindicated. When a delayed episode of hemorrhage occurred, the necessity of operation was avoided by the use of a gravity suit. In the meantime, renal failure was counteracted by means of peritoneal and renal dialysis. The other surviving patient was also treated with a gravity suit following an operation. The ability of the gravity suit to control hemorrhage, presumably by increasing the extraluminal pressure on bleeding vessels, has been reported on both an experimental and clinical basis.[12–14]

*Acute fatty metamorphosis with hepatic decompensation was responsible for 10 other maternal deaths in Los Angeles County during this time period. Nine of the patients had received tetracycline. None of these patients had convincing evidence of disseminated intravascular coagulation or other clotting deficiency.[11]

REFERENCES

1. Hakim-Elahi, E.: Obstet. Gynecol. **26:** 435, 1965.
2. McCrann, D. J., and Gaynon, R. A.: Conn. Med. **35:** 433, 1971.
3. Portnuff, J., and Ballon, S.: AM. J. OBSTET. GYNECOL. **114:** 1102, 1972.
4. Baird, J. N., and Hawley, R. G.: J. Reprod. Med. **6:** 93, 1971.
5. Owen, A., and Kandaloff, F.: J. Obstet. Gynaecol. Br. Commonw. **80:** 852, 1973.
6. Beecham, J. B., Watson, W. J., and Clapp, J. F.: Obstet. Gynecol. **43:** 576, 1974.
7. Lewis, R. T., Lodenquai, P., and Hall, J. St. E.: West Indian Med. J. **24:** 16, 1975.
8. Severino, L. J., Freedman, W. L., and Maheshikanar, A. P.: N. Y. State J. Med. **70:** 2818, 1970.
9. Ishak, K. G., and Rabin, L.: Med. Clin. North Am. **59:** 1001, 1975.
10. Slattery, L. R., Abrams, R. M., Beranbaum, E. R., Labow, S. B., and Aron, B.: Obstet. Gynecol. **32:** 664, 1968.
11. Mokatoff, R., Weiss, L., Brandon, L. H., and Camillo, M. F.: Arch. Intern. Med. **119:** 375, 1967.
12. Gardner, W. J., and Storer, J.: Surg. Gynecol. Obstet. **123:** 792, 1966.
13. Espinosa, M. H., and Updegrave, J. H.: Arch Surg. **101:** 36, 1970.
14. Cutler, B. S., and Daggett, W. M.: Am. Surg. **173:** 511, 1971.

Abnormality in metabolism of ^{15}N-labeled nitrate in toxemia

D. S. McLAREN
A. MROUEH
W. W. C. READ
Beirut, Lebanon

The urinary excretion of ^{15}N-labeled ammonium nitrate was studied during the last few weeks in patients with normal pregnancy and in those with toxemia. Marked diminution of the ^{15}N label was found consistently in patients with toxemia in the urinary fraction consisting of nitrogenous compounds other than urea and ammonia. The possible significance of this finding is discussed.

IT IS GENERALLY recognized that considerable retention of nitrogen occurs during pregnancy but, contrary to the early results obtained by inaccurate balance studies, it is now agreed that storage of protein in the human subject does not much exceed that accounted for by the fetus and maternal tissues and fluids.[2] In the rat, an early phase of protein anabolism is followed by a catabolic phase in late pregnancy coincident with rapid fetal growth.[3] As compared with that of the nonpregnant rat, nitrogen retention in the pregnant rat increases steadily throughout pregnancy and is accompanied by lowered levels of urea cycle enzymes in the liver and decreased urea excretion.[4] Evidence has been obtained that progesterone brings about these changes by diminishing adrenocorticosteroid secretion.[5]

Protein metabolism in other states of nutritional stress has been studied more extensively. By using ^{15}N-labeled ammonium citrate, it was shown that healthy infants receiving a low amount of protein utilize this nonessential form of nitrogen more efficiently than infants receiving a normal amount of protein and that it is built into such tissue proteins as albumin.[9] Using a similar technique in this laboratory, we were able to show that severely malnourished children fed a high-protein, high-energy diet reutilized a large proportion of dietary nonessential nitrogen and continued to do so for as long as three months after the high-protein diet was begun.[6]

The only previous study of ^{15}N-labeled compounds in pregnancy dealt with ^{15}N-glycine and demonstrated that with a low protein intake less label appeared in the urine in the form of urea than uric acid, suggesting more efficient utilization under nutritional stress.[7]

Our present interest was to see whether we could demonstrate any differences in the body's ability to metabolize nonessential nitrogen in the form of ^{15}N-labeled ammonium nitrate in abnormal pregnancy (especially toxemia) as compared with normal pregnancy.

Material and methods

Eight subjects were used in the experiments; two of them on two occasions. All were Lebanese adult women who were consuming their accustomed diet, which was nutritionally adequate. None showed any evidence of malnutrition. Several were overweight for their height.

Two subjects were healthy women, 22 and 38 years old, who were studied during the last few weeks of a normal pregnancy. Five subjects had toxemia of pregnancy as evidenced by blood pressure greater than 135/85 mm. Hg, albuminuria, and edema. Two of these five subjects were studied a second time; one was studied five months after delivery when she was normotensive, and the other was studied in a subsequent normal pregnancy. Another subject studied was a nonpregnant patient with hypertension related to an acoustic neuroma.

All subjects were ambulatory hospital patients, ad-

From the Nutrition Research Program and the Department of Obstetrics and Gynecology, American University Hospital, School of Medicine.

Partially supported by a grant from the School of Medicine, American University of Beirut.

Received and accepted for publication December 24, 1975.

Reprint requests: Dr. D. S. McLaren, Department of Physiology, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG.

Table I. Urinary nitrogen excretion in the form of urea plus ammonia in all study subjects

Case No.	Clinical state	Accumulative % excretion of ^{15}N as urea and ammonia: Hours after dose												Mean excretion of urea and ammonia (Gm. of nitrogen/24 hr.)
		3	6	9	12	15	18	21	24	36	48	60	72	
1	Normal pregnancy	11.0	19.6	28.7	34.8	38.8	42.1	44.6	48.9	57.7	61.5	63.9	66.4	5.63
2	Normal pregnancy	13.6	25.8	29.5	33.6	38.5	42.2	44.8	46.1	52.0	54.4	56.4	57.7	8.67
3	Toxemia	5.1	17.0	23.7	29.1	33.4	37.1	39.5	41.2	46.7	50.2	52.6	53.4	9.12
4A	Toxemia	10.9	17.6	25.4	30.9	34.0	35.6	37.1	39.7	44.6	46.1	48.4	49.8	5.81
5A	Toxemia	11.7	21.0	24.8	28.0	31.1	33.5	35.1	36.9	41.1	43.3	45.3	46.4	7.19
6	Toxemia	9.6	23.4	27.3	32.5	36.3	40.2	42.6	45.4	51.8	55.6	56.5	58.0	9.50
7*	Toxemia	3.7	12.2	17.6	19.4	22.4	25.6	27.7	31.4	–	–	–	–	4.31
4B	Nonpregnant (previous toxemia)	18.9	23.0	29.6	34.4	39.4	42.7	45.3	46.6	50.5	52.9	53.8	55.0	7.98
8	Nonpregnant, hypertensive	6.7	11.6	19.3	22.9	27.9	31.2	34.4	36.6	41.4	44.3	45.8	47.3	5.12
5B	Normal pregnancy (previous toxemia)	12.2	26.2	30.6	34.0	35.4	36.9	37.4	38.1	41.1	41.7	42.2	42.4	6.77

*Urine samples from this subject were complete only for the first day of the test period. The excretion figures in the last column are for this day only.

mitted to the hospital at least two days before the test began. They ate the normal hospital diet, and no medications were given during the course of the study.

On the first day of the test period, each patient was given orally a solution of ^{15}N-labeled (50 per cent isotope in the ammonium ion) ammonium nitrate, dissolved in 200 ml. of water. This was equivalent to 70 mg. of ^{15}N. The test solution was followed immediately by the first meal of the day. There was no restriction of fluid intake during the three days of the test period.

Pooled urine samples were collected at 3, 6, 9, 12, 15, 18, 21, 24, 36, 48, 60, and 72 hours after the solution was given. Stool was not collected as it is almost impossible to collect such samples with no contamination from urine in female subjects unless catheterization is used. We wished to avoid this. The error introduced by lack of stool samples is very small, ammonium salts being very efficiently absorbed from the gut.

Each sample was analyzed for total nitrogen, ammonia, and urea by standard procedures and for the ^{15}N content of each fraction by previously described methods.[6] Isotope measurements were carried out with an M.S. 10 mass spectrometer.

Results

The results are shown in detail in Tables I and II. Excretion of ^{15}N in the urea and ammonia fraction varied widely between subjects, but there was no difference between that of the toxemic group (mean excretion after 72 hours, 51.9 per cent ± 4.97 S.D.) and that of the nontoxemic group (53.8 per cent ± 9.32 S.D.). Unlabeled nitrogen excreted in these compounds was also similar (7.91 ± 1.72 and 6.83 ± 1.51 S.D. Gm. per 24 hours, respectively).

The toxemic group excreted a significantly ($p = 0.005$) smaller amount of the ^{15}N in forms other than urea and ammonia (3.8 per cent ± 2.51 S.D. during 72 hours) than the other group (13.7 per cent ± 4.36 S.D.). Excretion of unlabeled nitrogen in these forms was also significantly lower ($p = 0.05$) in the toxemic group (1.59 ± 0.64 S.D. Gm. per 24 hours) than in the other group (2.22 ± 0.08 S.D. Gm. per 24 hours), but the difference was smaller than for ^{15}N.

Comment

The etiology of the toxemic process in pregnancy and the eclampsia that ensues in the most severe cases is quite obscure. A wide variety of biochemical abnormalities has been reported, including the presence of various pressor substances.[10] Many of these findings have remained unconfirmed, and most do not help to clarify the nature of the underlying metabolic disturbance. To our knowledge, the metabolism of nitrogenous compounds has not previously been investigated.

The data presented here are for the accumulative percentage excretion of ^{15}N in the urea-plus-ammonia fraction (Table I) and in the non–urea-plus-ammonia fraction (Table II) in urine, together with the mean daily total nitrogen excretions of these respective fractions, expressed in grams of nitrogen per 24 hours.

In comparison with the values in the literature[1] for daily urinary nitrogen excretion in normal nonpregnant adults, all our subjects showed very low excretion, especially of urea, in some cases amounting to only

Table II. Urinary nitrogen excretion in forms other than urea and ammonia in all study subjects

Case No.	Clinical state	*Accumulative % excretion of ^{15}N not as urea or ammonia: Hours after dose*												*Mean excretion in other forms (Gm. of nitrogen/24 hr.)*
		3	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*36*	*48*	*60*	*72*	
1	Normal pregnancy	5.0	5.7	7.0	8.0	9.1	9.1	9.3	9.4	11.1	11.9	12.2	12.5	2.24
2	Normal pregnancy	1.3	2.7	3.5	4.3	5.2	5.9	6.7	7.9	7.9	9.0	10.3	11.0	2.35
3	Toxemia	0	0	0.1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.79
4A	Toxemia	0.1	0.2	0.2	0.3	0.5	0.8	1.1	1.5	1.5	2.6	2.7	3.2	1.36
5A	Toxemia	1.0	1.6	1.7	1.9	2.2	2.4	2.5	2.5	4.0	5.2	5.2	5.5	2.14
6	Toxemia	0.2	0.4	0.4	0.9	1.6	2.1	2.6	2.6	4.3	4.4	4.9	6.0	2.08
7*	Toxemia	0.1	0.1	0.3	0.4	0.7	0.7	0.9	0.9	–	–	–	–	1.40
4B	Nonpregnant (previous toxemia)	3.7	4.4	5.7	7.1	8.7	9.7	10.0	10.7	11.2	11.6	12.1	12.4	2.23
8	Nonpregnant, hypertensive	1.0	2.7	7.1	9.4	11.9	13.0	14.8	15.9	16.6	17.1	19.8	21.4	2.15
5B	Normal pregnancy (previous toxemia)	1.8	2.9	4.5	5.3	5.9	6.2	6.3	6.6	8.4	9.2	10.2	11.2	2.15

*Urine samples from this subject were complete only for the first day of the test period. The excretion figures in the last column are for this day only.

about half of the normal minimum value. This may have been in part due to the composition of the local diet which is very high in carbohydrate, known to be protein sparing. Moreover, pregnancy would be expected to cause considerable nitrogen retention. The fact that the amount of nitrogen excreted in the form of compounds other than urea and ammonia was within normal limits for all except three of the subjects indicates that this could not have been due to faulty sample collection. The results are consistent with those obtained in the rat in late pregnancy.[4]

The most significant finding in the present study was a consistent failure of the subjects with toxemia to incorporate the ^{15}N label into the non–urea-plus-ammonia fraction of the urine (0.5, 3.2, 5.5, 6.0, and 0.9 per cent) compared with the subjects with normal pregnancy (11.0 and 12.5 per cent) (Table II). Incorporation of the ^{15}N label into the larger urea-plus-ammonia fraction was similar in the two groups (Table I).

The results obtained in Cases 4B, 5B, and 8 provide additional information on the nature of the abnormality. The abnormality was shown in Case 4 when the patient was studied during the last few weeks of a pregnancy in which toxemia existed (Case 4A). Five months after delivery, she was studied again (Case 4B). At this time she was normotensive, fully healthy, and breast-feeding her baby. The incorporation of ^{15}N into the non–urea-plus-ammonia fraction was 12.4 per cent (compared with 3.2 per cent previously).

In Case 8, the patient had hypertension unrelated to toxemia. She was not pregnant at the time of the study. The incorporation of ^{15}N was 21.4 per cent.

In Case 5, the patient was studied a second time during a normal pregnancy (Case 5B) when 11.2 per cent incorporation occurred. The result during the previous toxemic pregnancy was only 5.5 per cent (Case 5A).

These results suggest that the abnormality is related to the toxemic state, that it disappears when that state is no longer active, and that it is not related to hypertension per se. A pregnant diabetic patient similarly studied did not show the abnormality, suggesting a relationship with toxemia specifically and not just any abnormal state in pregnancy.

The results permit some speculation to be made regarding the nature of the abnormality. The urine of all subjects showed similar amounts of ^{15}N in the urea-plus-ammonia fraction, suggesting that the major part of the metabolism of ammonia nitrogen is unaffected by the clinical state. However, excretion of ^{15}N in the other fraction of the urine, which consists of a mixture of many nitrogenous compounds, most of which are in very low concentrations, was greatly reduced in the patients with toxemia. This cannot be accounted for by the lowered excretion of unlabeled nitrogen in this fraction, which occurs to some extent in all the toxemic patients, because even in those patients with nitrogen excretion in the fraction close to normal the degree of labeling was very low compared to that in nontoxemic patients. Since it is unlikely that all the components of the non–urea-plus-ammonia fraction are equally affected, it seems probable that one compound or a group of closely related compounds, normally derived from ammonia nitrogen, is excreted in reduced amounts in toxemia.

REFERENCES

1. Documenta Geigy: Scientific Tables, ed. 6, New York, 1962 Geigy Pharmaceuticals.
2. Hytten, F. E., and Leitch, I.: The Physiology of Human Pregnancy, ed. 2, Oxford, 1971, Blackwell Scientific Publications, p. 357.
3. Naismith, D. J.: The foetus as a parasite, Proc. Nutr. Soc. **28:** 25, 1969.
4. Naismith, D. J., and Fears, R. B.: Adaptation in the metabolism of protein during pregnancy in the rat, Proc. Nutr. Soc. **31:** 8A, 1972.
5. Naismith, D. J., and Ritchie, C.: The protein cost of pregnancy in the rat, Proc. Nutr. Soc. **32:** 1A, 1973.
6. Read, W. W. C., McLaren, D. S., Tchalian, M., and Nassar, S.: Studies with ^{15}N-labeled ammonia and urea in the malnourished child, J. Clin. Invest. **48:** 1143, 1969.
7. Seitchik, J., and Alper, C.: Effect of dietary protein intake on metabolism of N15-labelled glycine in pregnant women, Surg. Forum 451, 1956.
8. Sheehan, H. L., and Lynch, J. B.: Pathology of toxemia of pregnancy, Edinburgh, 1973, J. & A. Churchill, Ltd.
9. Snyderman, S. E., Holt, L. E., Jr., Dancis, J., Roitman, E., Boyer, A., and Balis, M. E.: "Unessential" nitrogen: a limiting factor for human growth, J. Nutr. **78:** 57, 1962.
10. Vorne, M. S., Järvinen, P. A., Järvi, J., Ylostalo, P. R., and Kärki, N. T.: Pressor substances in the posthemodialysis dialysates of patients with toxemia of pregnancy, AM. J. OBSTET. GYNECOL. **119:** 610, 1974.

Fifth Annual Seminar: New Horizons in Perinatal Intensive Care

The Fifth Annual Seminar: New Horizons in Perinatal Intensive Care will be presented October 25 and 26, 1976, at the Los Angeles Marriott Hotel. It is sponsored by the Departments of Obstetrics/Gynecology and Pediatrics, Harbor General Hospital. The Course Directors are Donald M. Okada, M.D., Assistant Professor of Obstetrics and Gynecology, and Rosemary D. Leake, M.D., Associate Professor of Pediatrics. Thirteen hours of credit in Category 1 (formal) will be given by the California Medical Association. The fee for nurses is $85.00, and the fee for physicians is $135.00. Some of the major topics include: (1) Practical Aspects of Genetics, (2) Management of Hypertensive Pregnancies, (3) Fetal Asphyxia and Its Consequences, (4) Newborn Shock, (5) Immunological Aspects of Pregnancy, and (6) Tests Used for Evaluation of Placental and Fetal Well-being. The Guest Faculty include: Alfred W. Brann, Jr., M.D., Professor of Pediatrics, Division of Newborn Medicine, Emory University, School of Medicine, Atlanta Georgia; Richard H. Paul, M.D., Associate Professor of Obstetrics/Gynecology, USC School of Medicine, LAC/USC Medical Center; Roderick H. Phibbs, M.D., Associate Professor of Pediatrics, UCSF School of Medicine; and James R. Scott, M.D., Associate Professor of Obstetrics/Gynecology, University of Iowa.

For information and registration, contact: Robin J. Grant, M.P.H., Coordinator, Continuing Education, Professional Staff Association, 1124 W. Carson St., Torrance, California 90502. Telephone: (213) 328-2380, Ext. 1373.

Mead Johnson announces

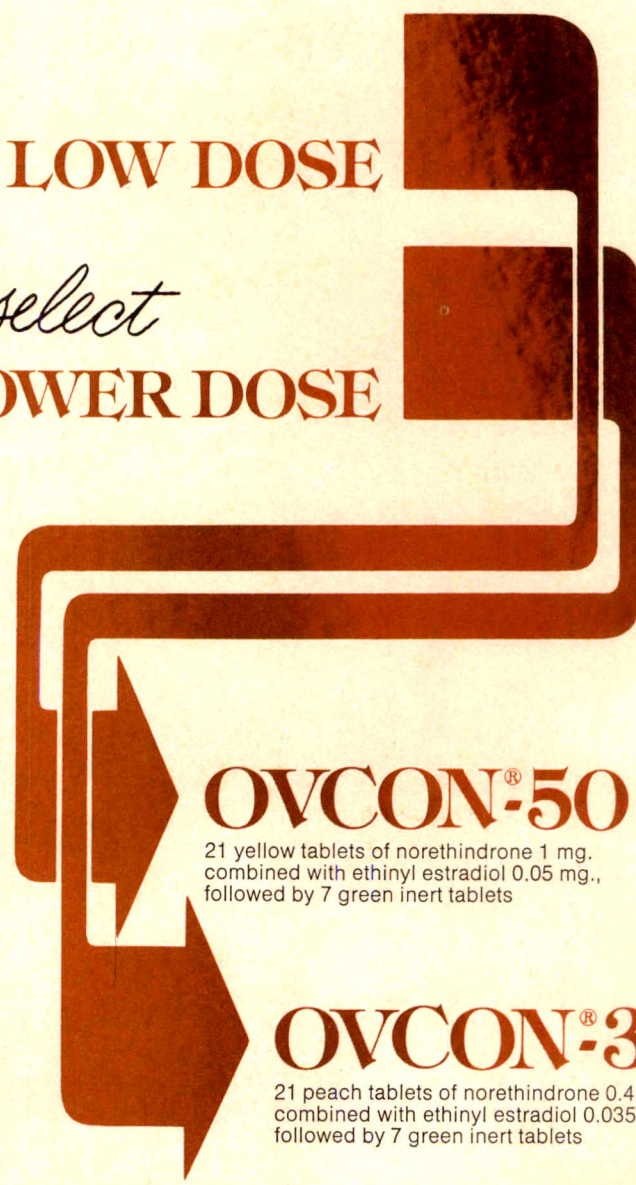
OVCON®

one name to remember
in low-dose oral contraceptives

two doses
from which to select

LOW DOSE

LOWER DOSE



OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

OVCON®-35*

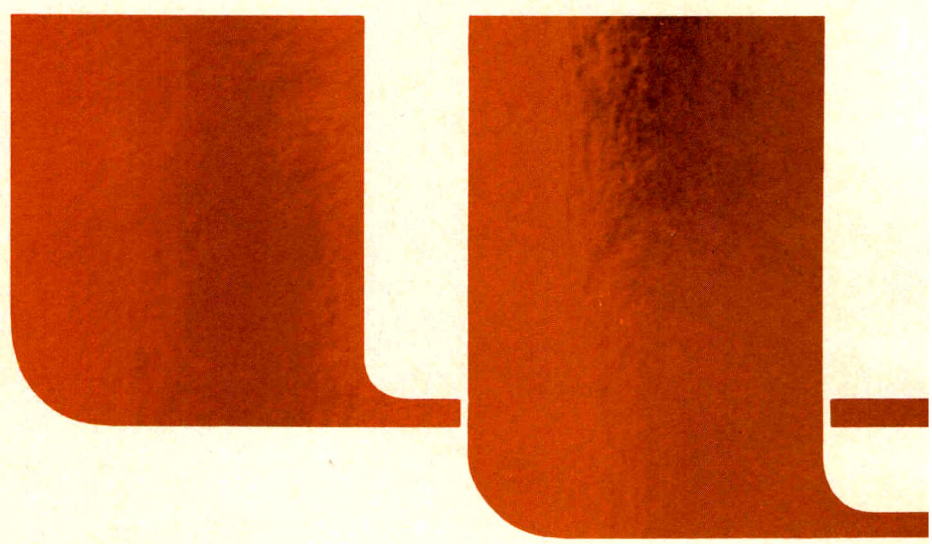
21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

For Brief Summary, please see last page of this advertisement.

One name to remember in combination oral contraceptive effectiveness...

OVCON®

two doses from which to select



providing...

- effective low-dose contraceptive protection*
- low incidence of common side effects†
- acceptable cycle control†
- in-depth clinical studies in widely different populations

Mead Johnson LABORATORIES

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

tested in 1,028 women for 9,558 cycles[1]

Although these women represented a wide range of socioeconomic groups with inherent differences in motivation, pregnancy rate (Pearl's formula) was 0.13 pregnancies per 100 woman years due to method failure and 0.75 pregnancies per 100 woman years due to patient failure. This results in a use-effectiveness of 0.88 pregnancies per 100 woman years.

Few women—2.7%—discontinued therapy for cycle-related reasons . . . and these were not necessarily spotting or breakthrough bleeding, but included amenorrhea and what women considered bleeding too little or too much. There was a discontinuation rate of 10.8% for all other on-therapy conditions, which, however, were not necessarily caused by Ovcon-50.

OVCON®-35*

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

tested in 1,861 women for 20,230 cycles[1]

In these women, with a wide range of backgrounds and motivations, there was effective control of conception. Pregnancy rate (Pearl's formula) due to method failure was 0.41 pregnancies per 100 woman years, and 0.95 pregnancies per 100 woman years were due to patient failure. This results in a use-effectiveness of 1.36 pregnancies per 100 woman years.

There was a higher discontinuation rate —11.6%—for cycle-related reasons with Ovcon-35 than with Ovcon-50, but, again, reasons included any spotting as well as amenorrhea and bleeding too much, too little, or irregularly. On the other hand, the discontinuation rate for all other on-therapy conditions, which were not necessarily related to Ovcon-35, was quite low—7.1%.

1. Data on file, Mead Johnson Laboratories.

OVCON-50 and OVCON-35* offer the advantages of effective low-dose protection and of uninterrupted regimens— 21 active tablets and 7 inert tablets

For Brief Summary, please see following page.

*The effectiveness of Ovcon-35 is somewhat lower than higher-dose combination products.

†See "Special Note" section of prescribing information on last page of this advertisement.

two dosages from which to select

LOW DOSE
OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets.

LOWER DOSE
OVCON®-35

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. The effectiveness of OVCON-35 is somewhat lower than higher-dose combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons due to menstrual disorders and irregularities appears to be higher for OVCON-35 than that observed with higher-dose combination products. An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Oral contraception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen dependent neoplasia; undiagnosed abnormal genital bleeding; known or suspected pregnancy.

Warnings: If signs of thrombotic and thromboembolic disorders (thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis) occur or are suspected, use of the drug should be discontinued immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug use was discontinued and not enhanced by long-term use.[1-10]) If gradual or sudden, partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11-13] Safety of use in pregnancy has not been established, therefore pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant cannot be determined at this time. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in short-term as well as long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

Precautions: A thorough history and physical examination of breasts and pelvic organs should include Papanicolaou smears. (Estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after the drug has been withdrawn for two months. Under the influence of these drugs, pre-existing uterine fibromyomata may increase in size. Some conditions (epilepsy, migraine, asthma, cardiac or renal dysfunction) might be influenced by fluid retention. Observe carefully for such. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged OVCON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. Diabetic patients should be carefully observed while receiving such therapy. The age of the patient constitutes no absolute limiting factor, although these drugs may mask the onset of the climacteric. The pathologist should be advised of OVCON therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. If cholestatic jaundice occurs, OVCON should be discontinued. This condition is more likely to occur in patients with a history of cholestatic jaundice of pregnancy.

Adverse Reactions Observed in Patients Receiving Oral Contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage and gall bladder disease. Suggestive evidence, neither confirmed nor refuted, between use and: neuro-ocular lesions (retinal thrombosis and optic neuritis) and hepatic lesions with or without intra-abdominal bleeding. Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps and bloating), breakthrough bleeding, change in menstrual flow, spotting, amenorrhea during and after treatment, breast changes (tenderness, enlargement and secretion), mental depression, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals, edema, chloasma or melasma (which may persist), cholestatic jaundice, migraine, rash (allergic). Reported association with use, neither confirmed nor refuted: anovulation post treatment; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; intolerance to contact lenses; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; vaginitis. *May Alter Laboratory Results in:* Hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X, decrease in anti-thrombin III and an increase in norepinephrine-induced platelet aggregability), thyroid function (increase in PBI, and butanol extractable protein bound iodine and decrease in T_3 uptake values), metyrapone test, pregnanediol determination.

References: (1) Royal College of General Practitioners: Oral contraception and thromboembolic disease. J. Coll. Gen. Pract. *13*:267-279, 1967. (2) Inman, W.H.W. and Vessey, M. P. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women in child-bearing age. Brit. Med. J. *2*:193-199, 1968. (3) Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease: A further report. Brit. Med. J. *2*:651-657, 1969. (4) Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. Thromboembolism and oral contraceptives: An epidemiologic case-control study. Amer. J. Epidem. *90*:365-380, 1969. (5) Oral contraception and increased risk of cerebral ischemia or thrombosis. New Eng. J. Med. *288* (17):871-877, 1973. (6) Oral contraceptives and stroke in young women. JAMA *231*(7):718-722, 1975. (7) Boston Collaborative Drug Surveillance Programme. Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumours. Lancet *1*:1399-1404, 1973. (8) Oral Contraceptives and Health. A summary of an interim report from the oral contraception study of the Royal College of General Practitioners, May, 1974. (9) Vessey, M. P., Doll, R., Fairbairn, A. S., and Glober, G. Post-operative thromboembolism and the use of oral contraceptives. Brit. Med. J. *3*:123-126, 1970. (10) Greene, G. R. and Sartwell, P. E. Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am. J. Public Health *62*:680-685, 1972. (11) Nora, A. H. and Nora, J. J. A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch. Envir. Health *30*:17-21, 1975. (12) Janerich, D. T., Piper, J. M., and Glebatis, D. M. Oral contraceptives and congenital limb-reduction defects. New Eng. J. Med. *291*(14):697-700, 1974. (13) Carr, D. H. Cytogenetics and malformations in abortions. Fed. Proc. *30*:102-103, 1971.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 754095

offer your staff new insights gathered from the experiences of their colleagues

A New Book!

CURRENT PRACTICE IN PEDIATRIC NURSING

Written by nurses with a variety of educational backgrounds, experience, and occupational goals, this collection of contemporary articles depicts personal experiences illustrating effective therapeutic strategies. Divided into three parts: Section I focuses on new attitudes in the roles, theories, and tools of pediatric nurses; Section II deals with family needs during fetal development and early childhood, and Section III is devoted to theories, methods, and studies of nursing care of children with special problems. These articles offer your staff the most current, descriptive, and accessible guidelines now available in pediatric nursing.

Edited by Patricia A. Brandt, R.N., M.S.; Peggy L. Chinn, R.N., Ph.D.; and Mary Ellen Smith, R.N., M.S. February, 1976. 242 pages plus FM I-XIV, 6¾″ × 9¾″, 13 illustrations. Price: $10.50 (cloth); $7.50 (paper).

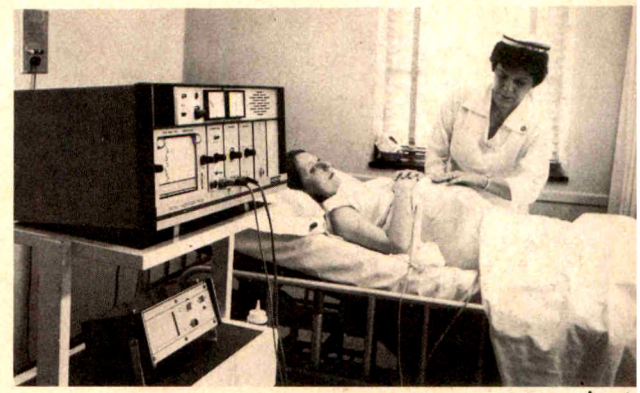
A New Book!

CURRENT PRACTICE IN OBSTETRIC AND GYNECOLOGIC NURSING

Designed specifically for professional nurses working with OB/GYN patients in communities and hospitals, this book offers original, dynamic articles focusing on relevant contemporary issues. Presenting a collection of different approaches contributed by experienced clinicians, these articles provide guidelines for the most current techniques available on prevention and care. Part I discusses theories, roles, and tools of maternity nursing; Part II explores physical and psychosocial needs during pregnancy and delivery; Part III examines fetal and neonatal care; Parts IV and V feature decisions of parenthood and abortion; Part VI details gynecologic surgery; and Part VII presents current teaching strategies. A reference your staff will find most rewarding!

Edited by Leota Kester McNall, R.N., M.N. and Janet Trask Galeener, R.N., M.S.; with 19 contributors. February, 1976. 254 pages plus FM I-XVI, 6¾″ × 9¾″, 39 illustrations. Price: $10.50. (cloth); $7.50 (paper).

MOSBY
TIMES MIRROR
THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

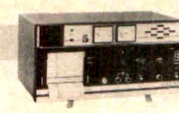


Intensive obstetrical care...

means reliable data on both fetal and maternal parameters from a Sonicaid FM3 monitor. A modular unit, it enables you to design your own ideal fetal maternal monitor. Inputs from both internal and external sources give you excellent flexibility in obtaining data during labor and delivery. Remote, central display links permit multi-patient scanning to optimize personnel use. For complete information, a demonstration, or trial, phone or write Executive Vice President John Scales today.

FM3 Modular Fetal/Maternal Monitor

visual and audio outputs, connections for remote displays and alarms, plus 4 maternal function monitors enable you to create an obstetrical data center for intensive care during labor and delivery.



SONICAID

P.O. Box 714 Fredericksburg, VA 22401 (703)898-6820 Telex 827304

Opportunity for an Obstetrician/Gynecologist to join two others in a multi-specialty group. Practice combines fee-for-service and pre-paid patients in a group which also includes Internists and Pediatricians. Opportunities for continuing education and teaching. Association with a voluntary, University-affiliated hospital. Please write or call Neil W. Garroway, M.D., Northeast Health Center, 905 Culver Road, Rochester, New York 14609, Phone: (716) 482-4300.

NEW Natafort®

COMPREHENSIVE PRENATAL VITAMIN FORMULA WITH MINERALS FROM PARKE-DAVIS

NATAFORT is a new, high-potency vitamin preparation with minerals, with special emphasis on the support *you* know is important for your pregnant patients.

- ■ *antianemia factors: iron and folic acid*
- ■ *calcium, 350 mg; and vitamin C*
- ☐ B-complex vitamins: niacinamide, vitamins B_1, B_2, B_6, and B_{12}
- ☐ other vitamins and minerals to help you support your patients' nutritional needs during pregnancy

Prescribe just one NATAFORT Tablet daily.

Each Natafort Tablet represents:

Vitamin A (acetate) (1.8 mg)	6,000 IU*
Vitamin D (ergocalciferol) (10 mcg)	400 IU
Vitamin C (ascorbic acid)	100 mg
Vitamin B_1 (thiamine mononitrate)	3 mg
Vitamin B_2 (riboflavin)	2 mg
Vitamin B_6 (pyridoxine hydrochloride)	15 mg
Vitamin B_{12} (cyanocobalamin) crystalline	5 mcg
Folic Acid†	1 mg
Nicotinamide (niacinamide)	15 mg
Vitamin E (*dl*-alpha tocopheryl acetate) (30 mg)	30 IU
Calcium (as calcium carbonate)	350 mg
Magnesium (as magnesium oxide)	1.7 mg
Iodine (as potassium iodide)	0.15 mg
Iron (as ferrous fumarate)	65 mg

Usual dose: One tablet daily

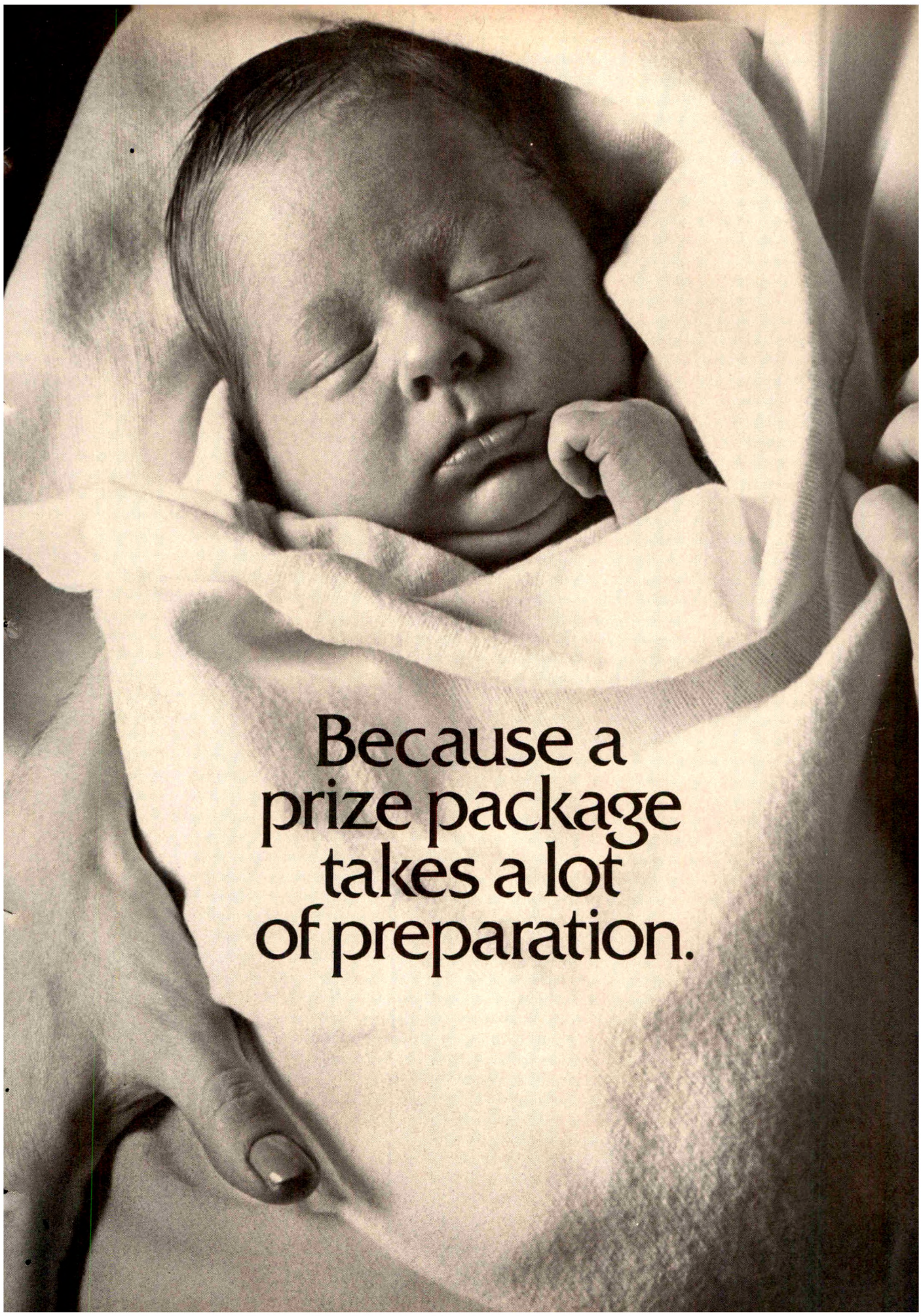
*IU=International Units

†CAUTION – Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.



PARKE-DAVIS

PARKE, DAVIS & COMPANY


Because a
prize package
takes a lot
of preparation.

ANTISEPTIC SECURITY

in Ob/Gyn practice

Prompt, broad-spectrum action of BETADINE Microbicides provides topical antiseptic security for patients, physicians and nurses

BETADINE Solution Microbicidal Applicator, the only 8½″ long, disposable antiseptic-impregnated swabstick, is indicated for degerming hard-to-reach sites, such as the cervix, vulvovaginal, perineal and anorectal areas

BETADINE Solution, for prepping skin, vagina and perineum, and for general antiseptic use on skin, mucosa and wounds

BETADINE Surgical Scrub, for preoperative scrubbing and for hand and skin degerming (In the rare instance of local irritation or sensitivity, discontinue use in the individual)

BETADINE Douche, for treating vaginal moniliasis, *T. vaginalis* vaginitis and nonspecific infectious vaginitis (*H. vaginalis* vaginitis)... also ideal for routine cleansing, due to its degerming and deodorizing properties

Purdue Frederick

© COPYRIGHT 1975, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A8076 168875



BETADINE® Microbicides

Foremost documented broad-spectrum topical microbicides



CHARLES C THOMAS · PUBLISHER

COLPOSCOPY: A Scientific and Practical Approach to the Cervix in Health and Disease (3rd Ptg.) *by* **Malcolm Coppleson**, *King George V Memorial Hospital, Sydney, Australia;* **Ellis Pixley**, *King Edward Memorial Hospital, Perth, Australia; and* **Bevan Reid**, *Univ. of Sydney, Sydney, Australia.* Deficiencies in the current methods of evaluation of the cervix in health and disease are discussed along with the scientific basis of colposcopy, including a detailed integration of colposcopic appearances with corresponding histology. In addition, the unique value of colposcopy in defining the precise sites of preclinical carcinoma and other epithelial conditions is graphically illustrated. *'76, 360 pp. (6 3/4 x 9 3/4), 225 il. (1 in color), 5 tables, $21.50*

AUGMENTATION MAMMOPLASTY *by* **A. Richard Grossman**, *Burn and Reconstructive Surgery Center, Sherman Oaks, California.* The prostheses mentioned in this text are the most common ones used today. The material encompasses discussions of surgical procedures of augmentation mammoplasty, currently marketed prostheses and the rationale for ongoing changes in their design and configuration, complications and their prevention and treatment, xerography, and the selection of patients and the psychosexual aspect of surgery. This book is specifically intended for the surgical resident, both in general and plastic surgery, and for the general surgeon who may not be as well versed in this procedure as some of his plastic surgeon contemporaries. *'76, 108 pp. (6 3/4 x 9 3/4), 141 il. (30 in color), $14.75*

CHEMOTHERAPY OF UROGENITAL TUMORS *by* **Gerald P. Murphy** *and* **Arnold Mittelman**, *Roswell Park Memorial Institute, Buffalo, New York. Foreword by* **Willet F. Whitmore, Jr.** *(4 Contributors)* This book presents a comprehensive review of past achievements in chemotherapy, presents uses and results of this therapy, and areas for future advancement. Each chapter features a realistic and critical evaluation of the clinical usefulness of chemotherapy in all stages and types of urogenital cancer, outlining representative programs. Within each disease category, criteria for evaluation of the clinical benefit of chemotherapy are presented and analyzed. The value of the multidisciplinary approach using chemotherapeutic agents as part of an integrated therapy is discussed for application in appropriate situations. *'75, 288 pp., 15 il., 62 tables, $24.50*

CANCER EPIDEMIOLOGY AND PREVENTION: Current Concepts *edited by* **David Schottenfeld**, *Memorial Sloan-Kettering Cancer Center, New York, New York. (23 Contributors)* A broad conceptual review of cancer epidemiology and prevention is provided in this text. The introductory section examines historical landmarks in cancer epidemiology, the magnitude of cancer and principles of the epidemiologic method and the concept of cause. Subsequent sections include chapters on screening and early detection and etiologic agents in man such as radiation, tobacco, sunlight and immunovirology. Various cancers are discussed including Burkitt's lymphoma, Hodgkin's disease, leukemia and cancers of the colon, rectum and uterine cervix. *'75, 592 pp. (6 3/4 x 9 3/4), 148 il., 86 tables, $45.50*

ARTIFICIAL INSEMINATION (2nd Ed.) *by* **Wilfred J. Finegold**, *Univ. of Pennsylvania School of Medicine, Pittsburgh. Foreword by* **Alan F. Guttmacher.** In dealing with this highly controversial subject, it is not the purpose of this book to propagandize but to inform. This completely revised Second Edition discusses both the pros and cons of artificial insemination, and covers the ethical, religious, legal and psychological ramifications of the procedure. This book will also clearly delineate those couples for whom artificial insemination is useless and those for whom it will be advantageous. Two major scientific advances are studied which have greatly increased acceptance of artificial insemination: the use of frozen sperm and the husband insemination procedure. *'76, 156 pp., $12.50*

CANCER GENETICS *edited by* **Henry T. Lynch**, *The Creighton Univ. School of Medicine, Omaha, Nebraska. (29 Contributors)* In this broad approach to cancer genetics, Doctor Lynch covers a wide range of problems associated with familial cancer. These include immunology; HL-A histocompatability system; oncogenic viruses; cytogenetics; migrant groups; nongenetic factors such as cigarette smoking, and their interaction with host factors in lung cancer etiology; xeroderma pigmentosum and other disorders associated with hereditary predisposition to cancer; and Wiskott-Aldrich syndrome neurocutaneous diseases. Genetic aspects of some of the more common cancers are also covered. Carcinoma of the colon, breast, lung, skin and stomach as well as hematologic malignancies are included. *'76, 656 pp. (6 3/4 x 9 3/4), 222 il., 106 tables, $49.50*

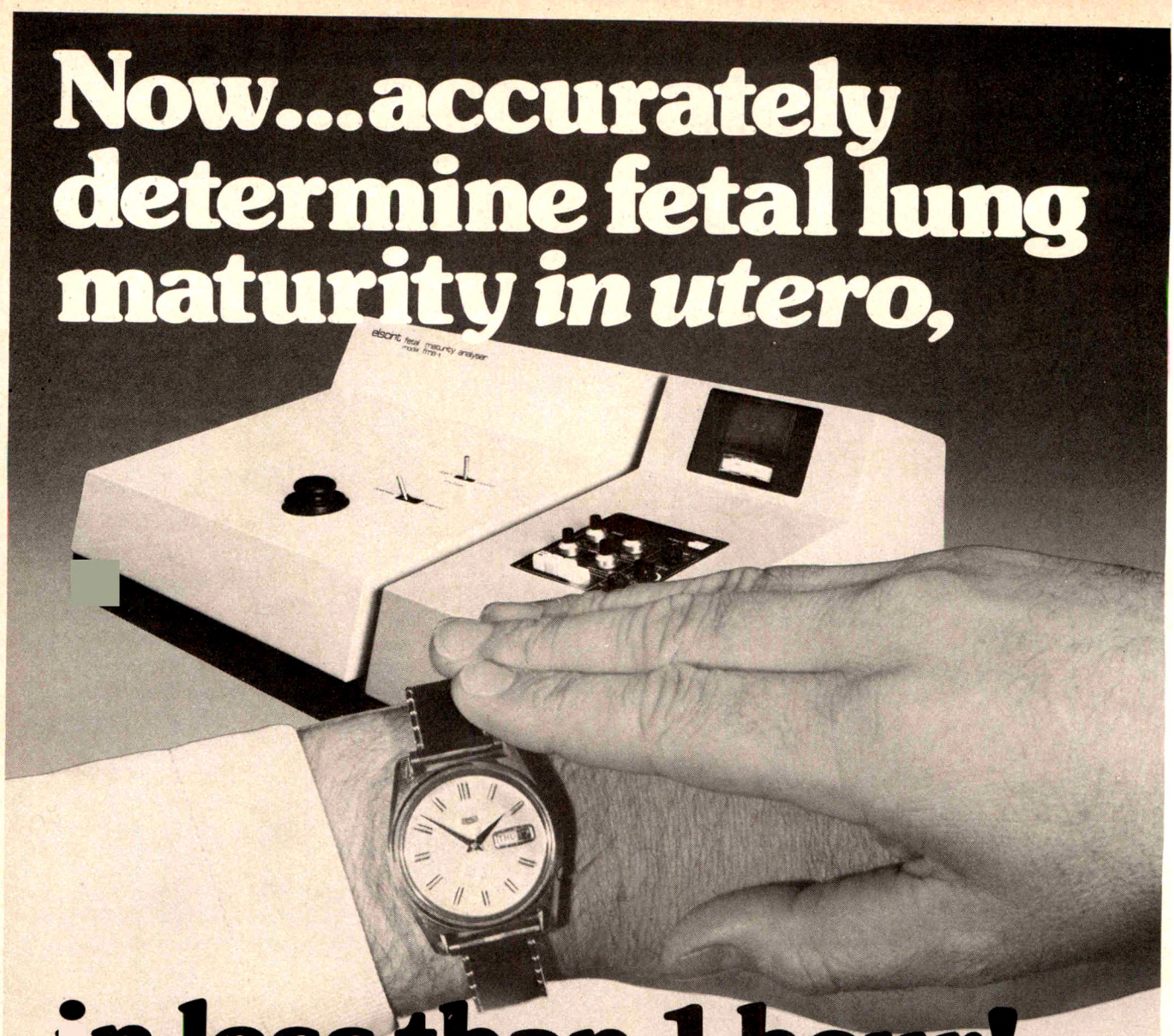
MOLECULAR PATHOLOGY *edited by* **Robert A. Good** *and* **Stacey B. Day**, *both of Sloan-Kettering Institute for Cancer Research, New York, and* **Jorge J. Yunis**, *Univ. of Minnesota Medical School, Minneapolis. (52 Contributors)* Presenting an interdisciplinary structure of concepts of disease at all levels of chemical and cytological architectural structure, this book discusses fundamental principles and primary mechanisms which can lead to enhancement of therapeutic programs and more specific treatment of disease states. The authors stress the need for investigation and analysis of disease processes at the subcellular (molecular) level and the perturbations of structure and function of organelles in health and in disease. *'75, 888 pp. (6 3/4 x 9 3/4), 259 il., 56 tables, $67.50*

NUTRITION AND OUR OVERPOPULATED PLANET *by* **Sohan L. Manocha**, *Emory Univ., Atlanta, Georgia.* Directed toward thinking people of all socioeconomic strata, this monograph highlights the nutritional requirements of various age groups and the relationship between the available food supply and the number of mouths laying claim to it. Readers will find the chapters on the nutritional needs of special age groups and the causes and effects of obesity and malnutrition both interesting and useful in helping to improve their concept of a balanced diet. Emphasis has also been placed on the nutritional needs of the adolescent and adult under normal and special conditions. *'75, 488 pp., 6 il., 11 tables, cloth-$24.50, paper-$16.75*

Orders with remittance sent, on approval, postpaid

301-327 East Lawrence Avenue • Springfield • Illinois • 62717

Now...accurately determine fetal lung maturity *in utero*,



...in less than 1 hour!

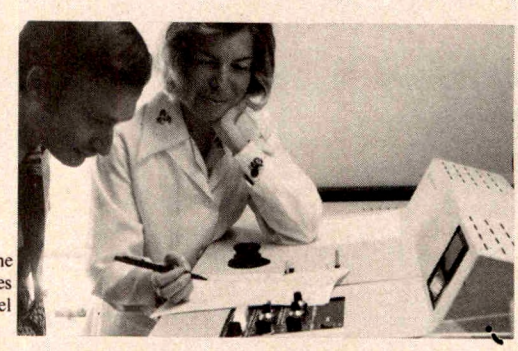
When an unborn life is in the balance, a fast precise lab test can make the crucial difference. The new Elscint FELMA (Fetal Lung Maturity Analyzer) can give you this important edge, quickly and accurately.

Designed to deliver fast, precise results in less than one hour, the FELMA is a highly sophisticated, clinically-proven * device requiring a simple clinical procedure — the extraction of as little as 0.5 ml. of amniotic fluid.

Because it's based on electro-optical principles, you get reliable, reproducible results each time Such accuracy will make easier those critical decisions about emergency steps which may be necessary.

The FELMA is a space-saver, too, requiring as little space as a desk. No special laboratory equipment is required; all that's needed to run the tests are a centrifuge and a small heating bath.

Call or write today for detailed information about this significant new development.



*Tested in the United States and Israel

Uncomplicated, no-delay operation!

Faster, simpler and more accurate than the L/S ratio test.

- Centrifuge amniotic fluid (10 min.).
- Add reagent (available from Elscint.).
- Incubate (20 min.).
- Cool (10 min.) at room temperature.
- Readout results on digital LED display.

elscint inc.

Where quality counts . . . count on Elscint.

P.O. Box 832; Hackensack, N.J. 07602 Tel. (201) 487-5885.

In United Kingdom: Elscint GB, 5 Priestley Way, Crawley Sussex RH102DW. Telephone: Crawley (0293) 21285/6/7. In France: Elscint S.A.R.L, 11 Rue Edouard-Lefebvre 78000 Versailles, Telephone: 950-2767. In Germany: Elscint GMBH, Freudenbergstrasse 27, 62 Wiesbaden-Schierstein, Telephone: (06121) 2786. In other countries: Write to Elscint Ltd., P.O. Box 5258, Haifa, Israel for the office in your country.

FETUS, PLACENTA, AND NEWBORN

Effect of ritodrine infusion on uterine and umbilical blood flow in pregnant sheep

RICHARD A. EHRENKRANZ, M.D.
ADRIAN M. WALKER, PH.D.
GARY K. OAKES, M.D.
MARGARET K. McLAUGHLIN, M.S.
RONALD A. CHEZ, M.D.
Bethesda, Maryland

The effect of ritodrine upon uterine artery blood flow (UtBF) and umbilical vein blood flow (UmBF) was investigated in near-term chronic sheep preparations. During intravenous ritodrine infusions to the ewe in sequential dose rates from 100 to 800 μg per minute, UtBF fell progressively to 43 per cent below control levels and mean maternal arterial pressure (MMAP) declined 20 per cent. During constant infusions of 100, 400, or 800 μg per minute of ritodrine to the ewe for 120 minutes, UtBF decreased 10, 37, and 31 per cent, respectively, and MMAP decreased 6, 20, and 25 per cent respectively. Dose-related maternal tachycardia and hyperglycemia occurred. There were no significant changes in UmBF, mean fetal arterial pressure, or fetal heart rate. During all infusions, maternal and fetal arterial pH, P_{CO_2}, and P_{O_2} remained within normal physiologic limits. Simultaneous infusion of ritodrine (400 μg per minute) and propranolol (100 μg per minute) blocked the maternal tachycardia, but decreases in UtBF, MMAP, and UmBF were observed. Ritodrine infusions to the fetus (25 μg per minute) resulted in fetal tachycardia and a variable increase in UmBF.

RITODRINE,* a beta-adrenergic agonist, is an effective inhibitor of both spontaneous and induced uterine contractions in human subjects.[1-6] There are associated cardiovascular and metabolic effects as well.[7] In human subjects, intravenous ritodrine infusions ranging from 50 to 600 μg per minute cause marked maternal tachycardia, slightly increased systolic blood pressure and moderately decreased diastolic blood pressure with resultant widening of the pulse pressure, a variable change in the fetal heart rate, and no adverse effect on maternal or fetal acid-base status.[1-6, 8] Since the response of the human uteroplacental circulation to ritodrine is unknown and cannot be determined, the present study was designed to evaluate its effects upon uterine artery and umbilical vein blood flow in near-term nonlaboring pregnant sheep. Changes in maternal and fetal blood pressure, heart rate, arterial blood gas, and glucose were also examined.

From the Pregnancy Research Branch, National Institute of Child Health and Human Development, National Institutes of Health.

Received for publication January 14, 1976.

Revised April 1, 1976.

Accepted May 10, 1976.

Reprint requests: Dr. Ronald A. Chez, NIH Clinical Center, Room 13N266, Bethesda, Maryland 20014.

**Ritodrine hydrochloride (also DU-21220 and Yutopar) was supplied by N. V. Philips-Duphar, Weesp , The Netherlands.*

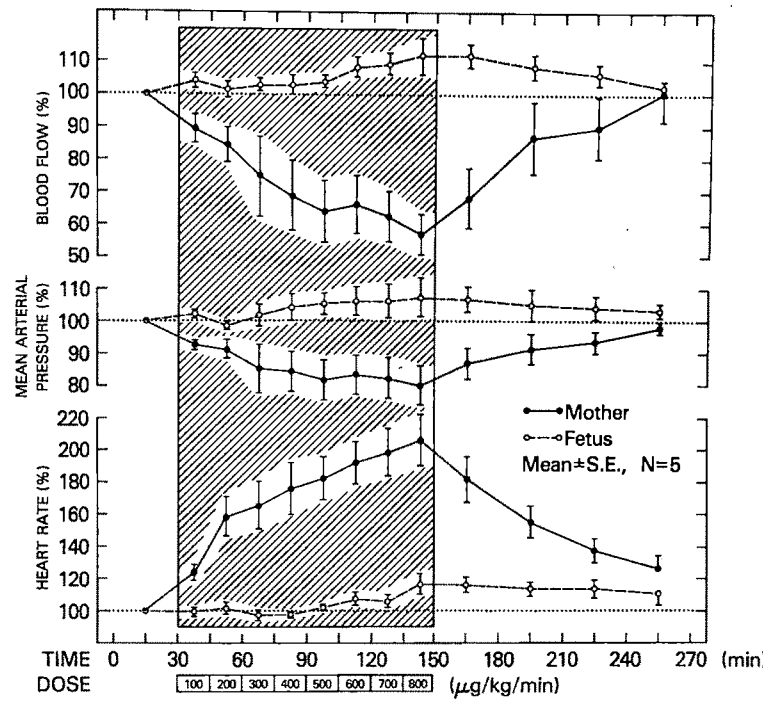


Fig. 1. Sequential ritodrine infusions to the ewe. Response (mean ± standard error) of UtBF, UmBF, MMAP, MFAP, MHR, and FHR during the ritodrine infusion, 100 to 800 μg per minute. Data are expressed as a percentage of control values.

Material and methods

Eight Dorset ewes, weighing 39 to 69 kilograms (51 ± 4 kilograms; mean ± standard error), with accurately timed singleton pregnancies were surgically prepared between 122 and 132 days of gestation (term = 145 ± five days). As described by Oakes and associates,[9] electromagnetic blood flow transducers* were applied to the main uterine artery of the pregnant horn and to the common intra-abdominal umbilical vein. Polyvinyl catheters were placed into the maternal aorta and inferior vena cava via superficial branches of the right femoral artery and vein, into the fetal abdominal aorta and inferior vena cava via hind limb vessels, and into the amniotic cavity. Following operation, the flow probe leads and the catheters, filled with heparinized saline, were exteriorized through a skin incision on the ewe's right flank and protected by a cloth patch bag.

Experiments were performed from the second to the thirteenth postoperative day at 124 to 140 days of gestation, while the ewe stood quietly in a metabolic cage. Uterine contractions were not present or induced. Only one experiment was done on an animal per day. All studies were performed with the same time course: a 30 minute control period, a 120 minute test period during which drugs were infused intravenously, and a 120 minute recovery period. A constant infusion rate of 2 ml. per minute of normal saline was used throughout maternal experiments; during the fetal infusion experiments, a rate of 0.2 ml. per minute in the test period was used.

The maternal dose range of ritodrine encompassed that studied clinically in human subjects, 50 to 600 μg per minute.[1-6] Four experimental groups were used.

Sequential ritodrine infusion to the ewe. During the test period, the ewe received a sequential ritodrine infusion beginning at 100 μg per minute increased to 800 μg per minute by 100 μg per minute increments every 15 minutes (No. = 5).

Constant ritodrine infusion to the ewe. During the test period, the ewe received a constant dosage of 100 μg per minute (No. = 5), 400 μg per minute (No. = 6), or 800 μg per minute (No. = 4).

Simultaneous ritodrine and propranolol infusion to the ewe. Two ewes who had received 400 μg per minute of ritodrine alone on previous days were infused simultaneously with 400 μg per minute of ritodrine and 100 μg per minute of propranolol during the test period.

Constant ritodrine infusion to the fetus. During the

*Micron Instruments, Inc., 1519 Pontius Ave., Los Angeles, California 90025.

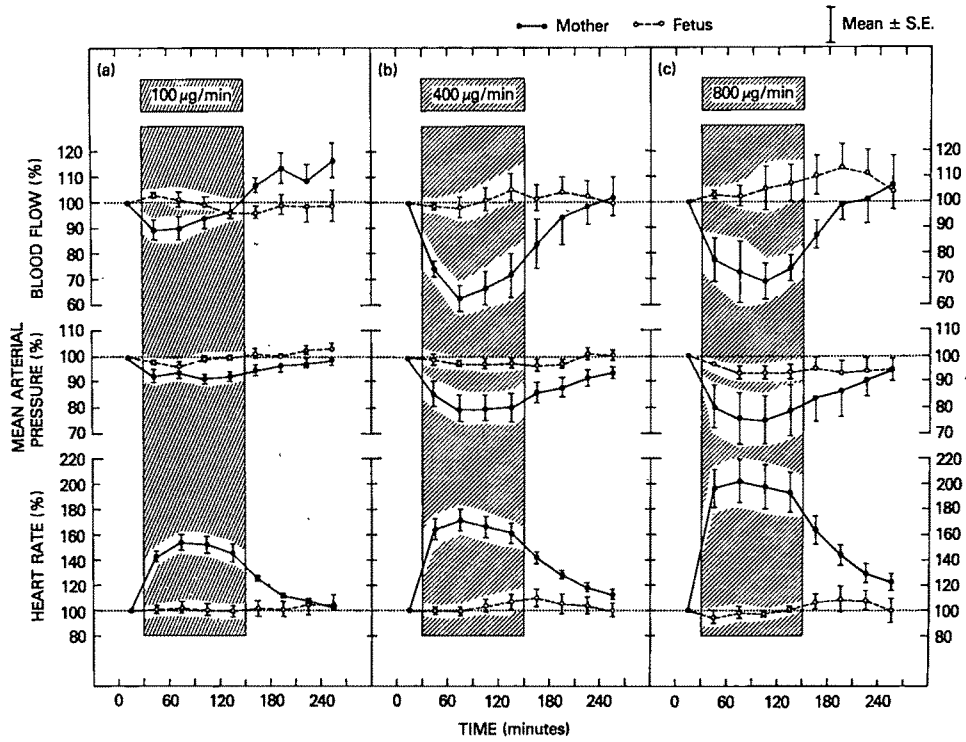


Fig. 2. Constant ritodrine infusions to the ewe. Response (mean ± standard error) of UtBF, UmBF, MMAP, MFAP, MHR, and FHR during infusions of *(a)* 100 μg per minute (No. = 5); *(b)* 400 μg per minute (No. = 6); *(c)* 800 μg per minute (No. = 4). Data are expressed as a percentage of control values.

test period, three fetuses received a constant infusion of 25 μg per minute (7.30 to 12.75 μg per kilogram).

During all experiments, main uterine artery and common umbilical blood flow were monitored continuously with flow meters with nonocclusive electronic zeroes*; the electronic zero was checked in vitro and in vivo and corresponded to true zero flow within 10 ml. per minute. Amniotic fluid and mean maternal and fetal arterial pressures were measured with pressure transducers† zeroed at the level of the ewe's heart. Mean fetal arterial pressure was corrected for variations in intrauterine pressure by subtracting the simultaneously measured amniotic fluid pressure. These indices were recorded simultaneously on an eight-channel rectilinear recorder.‡ Measurements of each of these indices were transcribed at five-minute intervals; also maternal and fetal heart rates were obtained every five minutes directly from their respective arterial tracings. Maternal and fetal arterial pH, Pco_2, and Po_2 were analyzed at 38.5° C.* Maternal and fetal glucoses were determined by a glucose oxidase method.†

To facilitate data analysis, each sequential infusion experiment was divided into 30 minute blocks during the control and recovery periods and 15 minute blocks during the drug infusion period, and each constant infusion was divided into nine 30 minute blocks. The mean measurement of each index in each time block was expressed as a per cent of the corresponding mean control value. The data from all the studies in each experimental group were then pooled, and Student's t test for paired data was used to test the significance of the changes.

Results

Sequential ritodrine to the ewe. The maternal and fetal measurements (mean ± standard error) are plotted against the drug infusion rate in Fig. 1. Uterine

*Micron RC1000, Micron Instruments, Inc.

†Statham P37B, Statham Instruments, Inc., 2230 Statham Blvd., Oxnard, California 93030.

‡Gould 200, Gould Inc., 18901 Euclid Ave., Cleveland, Ohio 44117.

*IL 513, Instrumentation Laboratory, Inc., 113 Hartwell Ave., Lexington, Massachusetts 02173.

†Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, California 92634.

Table I. Measurements during ritodrine infusion in the interval of maximum per cent decrease of UtBF (values are a per cent of the mean control value ± standard error)

Parameter	*Ritodrine infusion (dose)*		
	100 μg/min.	*400 μg/min.*	*800 μg/min.*
UtBF	90 ± 4*	63 ± 5†	69 ± 7*
MMAP	94 ± 2*	80 ± 5‡	75 ± 9*
MHR	154 ± 6†	171 ± 8†	197 ± 17†
UmBF	102 ± 3	98 ± 4	105 ± 8
MFAP	97 ± 2	98 ± 1	93 ± 2
FHR	102 ± 4	99 ± 3	98 ± 2

*$P < 0.05$.
†$P < 0.001$.
‡$P < 0.02$.

blood flow (UtBF) decreased progressively from control levels as the ritodrine dose increased, reaching 57 ± 6 per cent ($p < 0.01$) of the control value at 800 μg per minute. Mean maternal arterial pressure (MMAP) declined to 84 ± 6 per cent ($p < 0.05$) of the control level at 400 μg per minute and remained at about that level with further increments, being 80 ± 6 per cent ($p < 0.05$) of the control value at 800 μg per minute. Maternal heart rate (MHR) rose to more then twice control values as the dose rate increased to 800 μg per minute. At the end of the 120 minute recovery period, UtBF and MMAP were within 5 per cent of their control values; MHR had declined to 26 ± 8 per cent above control.

Constant ritodrine infusions to the ewe. Fig. 2 depicts the maternal and fetal measurements (mean ± standard error) plotted against the experimental time course. Table I lists the maternal and fetal data in the 30 minute interval of the constant ritodrine infusion experiments which demonstrated the maximum per cent decrease in UtBF. UtBF and MMAP decreased significantly during ritodrine infusions at each dose level. During constant infusions of 100, 400, or 800 μg per minute, UtBF fell 10, 37, and 31 per cent, respectively, and MMAP fell 6, 20, and 25 per cent, respectively. MHR demonstrated dose-related tachycardia during the constant ritodrine infusions, increasing 54 to 97 per cent.

During the last 30 to 60 minutes of the infusion, UtBF and MHR began to recover, but MMAP did not. By the end of the 120 minute recovery period, all measurements were near to or approaching control levels; an apparent increase in UtBF following the 100 μg per minute infusion of ritodrine was not significant.

Fetal changes during ritodrine infusion to the ewe. Fetal heart rate (FHR), umbilical blood flow (UmBF), and mean fetal arterial pressure (MFAP) measurements were not consistent during the sequential and constant ritodrine infusions to the ewe. The most frequent change, an elevation of FHR, to as much as 40 per cent above the control value, occurred in four of the five sequential infusion experiments and in eight of the 15 constant infusion experiments. UmBF increases of up to 40 per cent were noted in three of the five sequential infusion experiments and in five of the 15 constant infusion experiments. The remainder of the experiments showed small variable changes in UmBF. MFAP did not change significantly during any of the maternal infusion experiments. Although increases in FHR and UmBF at dose levels of 400 μg per minute of ritodrine or greater are suggested by the mean data (Figs. 1 and 2, *b*, and *c*), these trends were not statistically significant. Furthermore, during the 30 minute interval of maximum per cent decrease in UtBF (Table I), fetal measurements were not significantly altered.

Simultaneous ritodrine and propranolol infusion to the ewe. In comparison with the constant 400 μg per minute ritodrine infusion to these ewes, increases in MHR did not occur. However, UtBF and MMAP decreases of the same magnitude did occur. One ewe had a maximum per cent decrease of UtBF to 58 per cent of the control level with a corresponding fall of MMAP to 88 per cent of the control value, compared with decreases to 44 and 97 per cent of the control value, respectively, during the infusion with ritodrine alone. The second ewe had a maximum per cent decrease of UtBF to 66 per cent of the control level with a corresponding fall of MMAP to 92 per cent of the control level, compared with decreases to 51 and 79 per cent of the control value, respectively. UmBF declined steadily during the simultaneous infusion, reaching 76 and 87 per cent of the control level in the two fetuses, in contrast to the small variable UmBF changes noted during the experiments with 400 μg per minute of ritodrine alone. FHR and MFAP remained relatively constant.

Constant ritodrine infusion to the fetus. During the 25 μg per minute fetal ritodrine infusions, one fetus demonstrated UmBF increases ranging from 16 to 22 per cent above the control level, with UmBF remaining at that level through the recovery period; the second fetus had no change. UmBF measurements were not obtained in the third fetus. MFAP decreased slightly (6 to 8 per cent), and FHR was variable and irregular, with increases ranging from 12 to 39 per cent above the control value. No maternal changes were noted.

Biochemical studies. There were no significant changes in maternal or fetal arterial pH, P_{CO_2}, and P_{O_2}

during the sequential and constant maternal ritodrine infusion experiments, the simultaneous ritodrine and propranolol infusion experiments, and the constant fetal ritodrine infusion experiments.

Maternal and fetal plasma glucose levels rose during the constant maternal ritodrine infusions and continued to rise during the recovery period. With the 100 μg per minute infusion, maternal values increased from a control of 70 ± 3 mg. per cent by an average of 9 mg. per cent at the end of infusion and 21 mg. per cent at the end of recovery; fetal values increased from a control level of 14 ± 2 mg. per cent by an average of 4 and 5 mg. per cent, respectively. At the same time intervals, maternal values rose an average of 22 and 39 mg. per cent with the 400 μg per minute infusion, and an average of 38 and 50 mg. per cent with the 800 μg per minute infusion; fetal values rose an average of 5 and 11 mg. per cent and an average of 6 and 14 mg. per cent with those respective infusions. During the sequential infusions, maternal plasma glucose increased from a control of 59 ± 7 mg. per cent by an average of 24 mg. per cent at the end of recovery; fetal levels increased from a control of 15 ± 3 mg. per cent by an average of 7 mg. per cent. During the fetal infusions of ritodrine, fetal plasma glucose increased from a control of 8 ± 1 mg. per cent by an average of 8 mg. per cent at the end of infusion and remained at that level during the recovery period; maternal levels did not change. In contrast to the maternal infusions of ritodrine alone, neither maternal nor fetal plasma glucose levels increased during the simultaneous ritodrine and propranolol infusions.

Comment

Ritodrine has been investigated in doses ranging from 50 to 600 μg per minute for periods of 30 minutes to three hours in nonpregnant women,[1] in women in labor at term,[2–4] and in premature labor.[5, 6] These studies reported a dose-related increase in MHR and a widening of the pulse pressure due to decreases in diastolic blood pressure with no change or small elevations of systolic pressure. An increase in maternal cardiac output and a decrease in peripheral resistance were also shown.[6] FHR was unchanged in three of the studies,[2, 4, 6] increased 10 per cent during simultaneous ritodrine and oxytocin infusion,[3] and increased 13 per cent after ritodrine infusion had continued for 130 minutes.[5] MMAP was calculated in only one[6] of these six clinical studies, and, although it was reported as unchanged, estimates of MMAP from blood pressure measurements given in three of the reports[1, 3, 4] indicate decreases of that index. Five[2–6] of these studies used ritodrine infusion rates of less than 300 μg per minute.

In this study we examined the effect of ritodrine infusion upon the UtBF and UmBF of pregnant, nonlaboring, near-term sheep over the dose range used in human subjects. The effects of ritodrine infusion on MHR, FHR, and MMAP in the pregnant ewe agrees with the reported clinical data from human subjects in labor. In our experiments, MHR was increased within 2.5 minutes of the onset of an infusion and demonstrated a dose-related elevation; FHR was variable but did not change significantly, and MMAP decreased.

UtBF and MMAP were found to decrease significantly during the maternal ritodrine infusions. Although a range of UtBF and MMAP changes was noted from ewe to ewe during the infusions, the direction of the change was consistent. This consistency was even more apparent in three ewes who received the sequential and each constant dose infusion.

Ladner and colleagues[10] and Greiss[11] have shown that the placental vasculature of the pregnant sheep uterus is normally almost maximally dilated. Therefore, administrastion of β-adrenergic agonists to pregnant ewes would be expected to cause little increase in total UtBF, since only the nonplacental vasculature would be capable of responding to those agents with vasodilatation. In these experiments we observed significant UtBF decreases, not increases, a finding partly accounted for by decreases in MMAP. However, during sequential ritodrine infusions, MMAP plateaued at about 80 per cent of the control level with dose rates greater than 400 μg per minute, while UtBF continued to decline to 57 per cent of control levels. In addition, three of the 15 constant ritodrine infusions demonstrated MMAP decreases of less than 5 per cent while UtBF decreased 16 to 56 per cent; one of these animals also had MMAP decreases of less than 5 per cent as UtBF decreased progressively to 48 per cent below control values during the sequential infusion. Thus, ritodrine infusions in these experiments increased uterine vascular resistance. Futhermore, there appeared to be a tendency for UtBF and MHR to recover during the last 30 to 60 minutes of the constant ritodrine infusion to the ewe (Fig. 2). This trend may be suggestive of a tachyphylactic response which might have been evident if the infusion had been longer than two hours. Factors producing the increased uterine vascular resistance and the tendency for recovery during late infusion are unclear from our investigations but may include angiotensin II[12] generated by β-adrenergic–induced renin release,[13] reflex sym-

pathetic adrenergic nervous activity[11] secondary to hypotension, or a specific drug effect.

Although no significant UmBF, FHR, or MFAP changes occurred during the maternal ritodrine infusions, UmBF and FHR tended to increase late in the infusion period or early in the recovery period with dose levels of 400 μg per minute or greater (Figs. 1 and 2, *b* and *c*). In order to clarify the fetal response to ritodrine, constant infusions to the fetus were performed. In one fetus UmBF increased 20 per cent, while no change occurred in the other. In each fetus FHR increased and MFAP fell slightly. Creasy and coworkers[14] also found fetal tachycardia following intravenous ritodrine administration (0.3 to 6.0 μg per kilogram per minute) to the fetal lamb but reported no significant changes in cardiac output or placental blood flow with fetal administration and no alteration of FHR, MFAP, or fetal cardiac output with maternal infusions. Thus, the direct effects of ritodrine in the fetus provide indirect evidence of its placental transfer during maternal administration.

The simultaneous use of β-adrenergic agonist and a cardioselective β-adrenocepter blocker have been advocated as a means of blocking cardiovascular side effects and retaining uterine activity inhibitory effects.[15] In the two experiments in which ritodrine and propranolol were infused together, we observed normal MHR's but still noted decreases in UtBF and MMAP. Furthermore, UmBF decreased 13 and 24 per cent in the two experiments, whereas it did not change with ritodrine alone. Thus, simultaneous infusion of ritodrine and propranolol do produce cardiovascular effects which require further evaluation.

In these experiments, the ewes developed a relative acidemia. Fetal acid-base status remained within normal physiologic limits despite UtBF decreases as great as 50 per cent of control levels for periods as long as two hours. However, in order to comment with validity on the drug's safety for the fetal lamb, longer infusion periods are required.

Although there are limited data concerning the matabolic effects of ritodrine, other β-adrenergic agents have been shown to initiate glycogenolysis and lipolysis, resulting in increased levels of maternal blood glucose, lactate, and free fatty acids.[7] Recently, salbutamol also has been shown to produce a marked rise in plasma insulin levels of adult men.[16] The increases in maternal plasma glucose levels noted in our maternal infusion experiments probably result from ritodrine-induced glycogenolysis. While the fetal plasma glucose increases noted during those infusions most likely represent maternal-fetal placental transfer, fetal glycogenolysis is suggested by the elevation of fetal plasma glucose levels during the direct fetal infusions. The lack of maternal hyperglycemia during the simultaneous ritodrine and propranolol infusions is consistent with β-adrenergic–induced glycogenolysis.

The use of β-adrenergic agents for the treatment of premature labor and intrapartum fetal distress is currently being advocated. Although the appropriateness of extrapolating these data obtained in experiments with a nonlaboring pregnant animal preparation to human subjects in labor is not clear, evaluation of these agents in the pregnant sheep does allow examination of indices not presently measurable in the human subject.

REFERENCES

1. Coutinho, E. M., Bomfim de Sousa, M., Wilson, K. H., and Landesman, R.: Inhibitory action of a new sympathomimetic amine (DU-21220) on the nongravid uterus, Am. J. Obstet. Gynecol. **104:** 1053, 1969.
2. Landesman, R., Wilson, K. H., Coutinho, E. M., Klima, I. M., and Marcus, R. S.: The relaxant action of ritodrine, a sympathomimetic amine, on the uterus during term labor, Am. J. Obstet. Gynecol. **110:** 111, 1971.
3. Barden, T. P.: Effect of ritodrine on human uterine mobility and cardiovascular responses in term labor and the early postpartum state, Am. J. Obstet. Gynecol. **112:** 645, 1972.
4. Nochimson, D. J., Riffel, H. D., Yeh, S., Kreitzer, M. S., Paul, R. H., and Hon, E. H.: The effects of ritodrine hydrochloride on uterine activity and the cardiovascular system, Am. J. Obstet. Gynecol. **118:** 523, 1974.
5. Bieniarz, J., Motew, M., and Scommegna, A.: Uterine and cardiovascular effects of ritodrine in premature labor, Obstet. Gynecol. **40:** 65, 1972.
6. Bieniarz, J., Ivankovich, A., and Scommegna, A.: Cardiac output during ritodrine treatment in premature labor, Am. J. Obstet. Gynecol. **118:** 910, 1974.
7. Unbehaun, V.: Effects of sympathomimetic tocolytic agents on the fetus, J. Perinatal Med. **2:** 17, 1974.
8. Humphrey, M., Chang, A., Gilbert, M., and Wood, C.: The effect of intravenous ritodrine on the acid-base status of the fetus during the second stage of labour, J. Obstet. Gynaecol. Br. Commonw. **82:** 234, 1975.
9. Oakes, G. K., Ehrenkranz, R. A., Walker, A. M., and Chez, R. A.: Uteroplacental blood flow during hyperthermia with and without respiratory alkalosis, J. Appl. Physiol. In press.
10. Ladner, C., Brinkman, C. R., III, Weston, P., and Assali, N. S.: Dynamics of uterine circulation in pregant and non-pregnant sheep, Am. J. Physiol. **218:** 257, 1970.
11. Greiss, F. C., Jr.: Concepts of uterine blood flow, *in* Wynn, R. M., editor: Obstetrics and Gynecology Annual, New York, 1973, vol. 2, Appleton-Century-Crofts, Inc., p. 55.
12. Assali, N. S., Brinkman, C. R., III, and Nuwayhid, B.: Comparison of maternal and fetal cardiovascular func-

tions in acute and chronic experiments in the sheep, AM. J. OBSTET. GYNECOL. **120:** 411, 1974.
13. Leenen, F. H. H., Redmond, D. P., and McDonald, R. H., Jr.: Alpha and beta adrenergic-induced renin release in man, Clin. Pharmacol. Ther. **18:** 31, 1975.
14. Creasy, R. K., Siimes, A. S. I., Heymann, M. A., and Rudolph, A. M.: Effect of ritodrine of the fetal lamb, Gynecol. Invest. **6:** 14, 1974.
15. Barden, T. P., and Stander, R. W.: Myometrial and cardiovascular effects of an adrenergic blocking drug in human pregnancy, AM. J. OBSTET. GYNECOL. **101:** 91, 1968.
16. Goldberg, R., Van As, M., Joffe, B. I., Krut, L., Bersohn, I., and Seftel, H. C.: Metabolic responses to selective β-adrenergic stimulation in man, Postgrad. Med. J. **51:** 53, 1975.

Placental cultures for cytogenetic assessment in saline-aborted fetuses

H. ALLEN GARDNER, M.D., M.Sc., F.R.C.P.(C.)
E. MARTHA WOOD, B.A., R.T.
ELLYN STECKER, B.A.
Toronto, Ontario, Canada

Confirmation of cytogenetically abnormal fetuses following saline abortion has been shown to be possible with the placenta as the source of viable fetal cells. The method is described in detail. In one third of cultures, only female cells were present. Differentiation between maternal and female fetal tissue when no numerical or structural cytogenetic disorder is present requires detailed analysis of fluorescently stained chromosomes for polymorphisms.

THE DEVELOPMENT OF techniques for the antenatal detection of genetic diseases has proved to be a milestone in preventative medicine. Amniotic fluid taken at 16 weeks' gestation is analyzed in the laboratory and, by 19 weeks, a decision is possible concerning the state of the fetus. If an abnormality is detected, the family then can be offered a therapeutic abortion to prevent the birth of an abnormal child. Practical and theoretic difficulties may arise in the laboratory technology. If the fetus is female, one cannot be entirely sure that the cells examined have not come from the mother rather than the baby. In the case of chromosome mosaicism or genetic heterozygosity, it is possible that the normal cell line grew preferentially in culture to the disadvantage of the abnormal.

Thus, confirmation of prenatally detected abnormalities from tissue derived directly from the fetus is very important at this stage of our knowledge regarding amniocentesis. Without postabortion confirmation, there will be lingering doubts in the minds of both parents and physicians as to the validity of the prenatal diagnosis which determined that the abortion should be performed. This is a distinct disadvantage to the continued growth of the whole area of therapeutic abortion. When the abortion has been performed by hypertonic saline infusion, the abortus is a macerated fetus, and to date no report of successful culture of fetal cells has been published. Although it has been considered unlikely that any confirmation of a prenatal study could be performed on such a fetus, Lowden and associates[1] have been able to confirm the diagnosis of gangliosidosis in a saline-aborted fetus through direct enzyme analysis of tissue and electron microscopy[1]; Gardner and colleagues[2] and Kohn and co-workers[3] were successful in the use of placental cultures.

Therefore, it is of some importance to determine whether any viable tissue is present in an abortus which could be used to confirm the prenatal diagnosis. We anticipated that two major variables would enter into this problem: the length of time that the fetus was exposed to the saline environment and the length of time between death of the fetus and its expulsion.

It is believed that different tissues in the fetus would react differently to these variables. Cells in direct contact with the saline (fetal skin, umbilical cord, and fetal membranes) would be killed quickly. On the other hand, viscera may not be affected by the hypertonic saline but would certainly be influenced by postmortem autolysis which, in turn, is influenced by the length of time between the death of the fetus and the passing of the products of conception. The cells least likely to be affected by either the saline or autolysis were considered to be connective tissue cells located deep in the fetus.

From the Department of Pathology, Toronto General Hospital and the University of Toronto.

Supported by Ontario Ministry of Health Grant PR 279.

Received for publication March 8, 1976.

Revised June 3, 1976.

Accepted June 8, 1976.

Reprint requests: Dr. H. Allen Gardner, Head of Cytogenetics, Toronto General Hospital, 101 College St., Toronto, Ontario, Canada M5G 1L7.

Methods and material

Twenty-two saline-aborted fetuses were obtained following intra-amniotic injections of saline. Nineteen were aborted by the use of 20 per cent saline and three were aborted by 5 per cent saline infusion. The interval of time between the injection of saline and the passage of the products of conception ranged from 24 to 48 hours.

A number of tissues were prepared for in vitro culture, with emphasis on connective tissue deeply situated in the body, which we believed would best withstand saline and autolytic conditions. Eleven cultures were attempted with aorta; 12, with bone and cartilage; and two, with muscle. Twenty-four additional cultures were set up with other tissues: skin (eight), testis (two), kidney (four), lung (two), urine (one), heart (one), eye (one), liver (three), adrenal (one), and fingernail (one). In addition, on seven occasions, short-term lymphocyte cultures were attempted from thymus, spleen, and heart blood. Thus, a total of 56 cultures from 22 fetuses were initiated. Control tissue was obtained from hysterotomy-aborted fetuses.

The culture methods used were standard in this laboratory and were local modifications of established techniques.

Results

It was quickly established that control cultures of aorta, bone, muscle, and other tissues derived from hysterotomy-aborted fetuses had a rapid initiation of growth and good cell proliferation.

In none of the 56 cultures set up from the saline-aborted fetuses was there even the slightest evidence of growth. On the other hand, tissue derived from the placenta did show evidence of viability. Growth was poor, slow, and erratic, but, over a period of time, some specimens had sufficient growth to allow cytogenetic studies.

A histologic examination of placenta following saline abortion was made, and this suggested that, on morphologic grounds, there were sufficient viable cells to pursue this study further. Eventually the following method was established.

The placenta was obtained as soon after expulsion from the uterus as possible—although sometimes there was as much as a 24 hour delay. That portion chosen for culture was washed repeatedly in Hanks balanced salt solution until all traces of red cells had disappeared. This served also to wash away excess microorganisms.

The tissue culture medium used was Alpha medium containing penicillin and streptomycin and supplemented to 20 per cent with fetal calf serum. We found that our standard method for long-term culture, placing tiny pieces of tissue between two cover slips in a Leighton tube, did not work well with placenta.

Instead, the tissue was teased and torn until we obtained the nearest thing possible to a single cell suspension. This was then transferred into T30 flasks. Growth was usually evident by one week.

The site chosen for taking the cultures also was important. Chorioamniotic membrane and tissue adjacent to it failed to grow, probably because of their proximity to the effects of saline in the amniotic sac.

The placenta's maternal surface grew best but, as discussed later, cells were often only maternal in origin.

Tissue taken midway in the placenta was deemed to be the best for fetal monitoring. The maternal surface was scraped with a scalpel until the desired depth was reached. That portion of tissue was cut away and prepared for culture as described.

Cultures were handled in our routine way, and the medium was changed every three or four days. Both epithelial and fibroblastic cells grew. Harvesting was possible about three weeks after planting, but the cells reacted strongly to exposure to trypsin. Therefore, it was necessary that more cells than usual were present before beginning the harvesting technique.

In all, 56 placental cultures were initiated. Three controls derived from hysterotomies grew well. In 17, there was no growth, or contamination ensued. However, most of these failures occurred during the initial stages of the study and before our method became established. In the last 31 set up, only one culture failed to grow, thus establishing the viability of placental cells following 20 per cent saline abortion. In addition, cells from one prostaglandin-induced abortion, one spontaneous abortion, and one 5 per cent saline–induced abortion grew well.

To establish the extent of growth of maternal as well as fetal cells, placental cultures from male fetuses were reviewed. The sex of the fetus was confirmed by phenotype and/or histology. Of 27 male fetuses, three were aborted by hysterotomy; one, by 5 per cent saline infusion; and 23, by 20 per cent saline infusion. In nine, only fetal cells were observed in culture as evidenced by propagation of only 46,XY cells. In a further nine, two cell lines grew, one with a 46,XY complement and the other with a 46,XX complement. And, in nine other cultures, only 46,XX cells grew. Thus, in two thirds of placental cultures, it was possible to recognize and monitor fetal cells.

Comment

Intra-amniotic infusion of hypertonic saline is a widely used method of therapeutic abortion. Within a

few hours, not only does the conceptus die,[4] but also the fetal cells are killed, no matter where situated or what type. The survival of placental tissue is probably dependent on the ability of the maternal circulation to maintain not only maternal cell viability but also fetal cell viability. This is supported by the maintenance of electrolyte balance in the maternal serum despite the hypertonic load.[5–7] The determining factor regarding successful culture of placental tissue is probably the length of time between separation of the placenta from the uterine wall and its preparation for culture.

Although the placenta is fetal in derivation, its intimate contact with the uterus means that, when it is shed, maternal cells are admixed. This is borne out by those cultures where both 46, XY and 46, XX cells were found. One would suppose that the farther away from the maternal surface of the placenta the cells were obtained, the less likely it would be that maternal cells would be present. On the other hand, the closer to the fetal surface the cells are obtained, the greater is the influence of the saline, and the lesser is the viability of the tissue. There seemed to be no correlation between the ratio of fetal to maternal cells and the site from which the tissue was taken for culture.

When the fetus was male, there was no problem in identifying its cells, even if maternal cells grew along with them. In two thirds of our cases, it would have been possible to identify fetal cells if a fetal marker existed. In the present series, this marker was the Y chromosome. If the fetus is female, it would be necessary to rely on more obvious fluorescent markers to distinguish fetal from maternal cells.

During the time of this study, four patients who had clinical indications for postabortion or postnatal fetal monitoring were studied. All had successful placental cultures. In three patients, fetal monitoring via amniocentesis revealed trisomy 13[2]; a 5/16 translocation; and trisomy 21. All were aborted by saline at 19 weeks' gestation and, in all, the prenatal diagnosis was unequivically confirmed with placental culture. One stillborn macerated term male fetus with cyclopia proved to have 47,XY,+18 by this method.[8]

Viable placental cells have also been cultured from an intrauterine death of one month's duration and from other abortions, both spontaneous and therapeutic.

It is thus apparent that the placenta remains viable for a considerable length of time despite the state of the fetus. In some situations, placental culture offers the only alternative to assessing the cytogenetic state of the fetus. The assessment of inborn errors of metabolism from these cells must await more definitive definition of the biochemical profiles of placenta as compared to those of amniocytes and fibroblasts.

The authors are grateful to Dr. D. J. Gare, Department of Obstetrics and Gynaecology, Toronto General Hospital, for consultation, and to Miss Sandy Cox for typing.

REFERENCES

1. Lowden, J. A., Cutz, E., Conen, P. E., Rudd, N., and Doran, T. A.: Prenatal diagnosis of GMI-gangliosidosis, N. Engl. J. Med. **288:** 225, 1973.
2. Gardner, H. A., Rudd, N., and Benzie, R. J.: Confirmation of antenatally detected trisomy D from saline aborted products of conception, Lancet **1:** 751, 1974.
3. Kohn, G., Ornoy, A., and Cohen, M. M.: Prenatal diagnosis: A problem in vertification, J. Med. Genet. **11:** 247, 1974.
4. Kovacs, L., Resch, B., Sjollosi, J., and Herczeg, J.: The role of fetal death in the process of therapeutic abortion induced by intra-amniotic injection of hypertonic saline, J. Obstet. Gynaecol. Br. Commonw. **77:** 1132, 1970.
5. Pathak, U. N.: Induction of labor by intra-amniotic injections of saline, AM. J. OBSTET. GYNECOL. **101:** 513, 1968.
6. Frigoletto, F. D., and Pokoly, T. B.: Electrolyte dynamics in hypertonic saline-induced abortions, Obstet. Gynecol. **38:** 647, 1971.
7. Wong, T. C., Palav, A. B., Kim, B. J., and Tricomi, V.: Changes in serum and urinary electrolytes following intra-amniotic injection of hypertonic saline, N. Y. State J. Med. **72:** 564, 1972.
8. Lang, A. P., Schlager, F. M., and Gardner, H. A.: Trisomy 18 and cyclopia, Teratology. In press.

Umbilical cord compression associated with amniotomy: Laboratory observations

STEVEN G. GABBE, M.D.
BRUCE B. ETTINGER, M.D.
ROGER K. FREEMAN, M.D.
CHESTER B. MARTIN, M.D.
Los Angeles, California

Impairment of umbilical cord blood flow has been associated with periodic fetal heart rate changes termed "variable decelerations." These patterns may be observed after amniotomy. A chronic fetal rhesus monkey preparation has been used to investigate this clinical observation. Loss of amniotic fluid produced variable deceleration patterns, while restoration of amniotic fluid volume eliminated such changes. These experimental data demonstrate that amniotic fluid may be critical in protection of the cord and maintenance of normal umbilical cord blood flow.

IMPAIRMENT OF UMBILICAL CORD blood flow has been associated with periodic fetal heart rate (FHR) changes termed "variable decelerations."[1] These patterns are often observed when the cord is tangled about the fetus, is trapped between the fetus and uterine wall, or has prolapsed. Variable decelerations also may be seen after amniotomy. A chronic fetal rhesus monkey preparation has been used to investigate the association between amniotic fluid volume and variable decelerations.

Material and methods

The technique used to establish the chronic fetal rhesus monkey preparation has been previously described.[2] Instead of traversing the myometrium, the sampling catheters and electrode leads pass from the hysterotomy site, outside of the fetal membranes, through the cervical canal and vagina to the exterior. The estimated duration of pregnancy at operation ranged from 110 to 140 days.

From the Department of Obstetrics and Gynecology, University of Southern California.

Presented at the District VIII, Meeting of the American College of Obstetrics and Gynecology, Salt Lake City, September 21-24, 1975.

Received for publication October 24, 1975.

Revised April 12, 1976.

Accepted May 10, 1976.

Reprint requests: Dr. Steven G. Gabbe, LAC/USC Medical Center, Women's Hospital, Room 5K9, 1240 N. Mission Rd., Los Angeles, California 90033.

Results

It has been our repeated observation that opening the chorioamnion and allowing escape of amniotic fluid is associated with the onset of variable decelerations. Removal of approximately 75 c.c. of amniotic fluid, half of the normal intrauterine volume, or leakage of fluid along the catheter tract after operation will produce variable decelerations. A representative experiment is illustrated in Fig. 1. Infusion of normal saline solution and restoration of the amniotic fluid volume will markedly decrease the frequency of these decelerations.

Comment

Amniotic fluid has several important mechanical functions.[3] It provides constant lubrication between the fetus, umbilical cord, and membranes and assures unimpeded fetal mobility. Without an adequate fluid volume, adhesions between the amnion and parts of the fetus may result. Amniotic fluid also protects the fetus from external trauma and pressure by equalizing forces applied to the intrauterine contents.

The umbilical cord may be especially vulnerable to occlusion by external pressure if amniotic fluid volume is decreased. In antepartum contraction stress testing, patients with documented intrauterine growth retardation and oligohydramnios may demonstrate FHR patterns of profound cord compression with minimal uterine activity.[4] Caldeyro-Barcia and associates[5, 6] have stressed the protective effects of an intact bag of waters during labor. They noted that amniotomy dis-

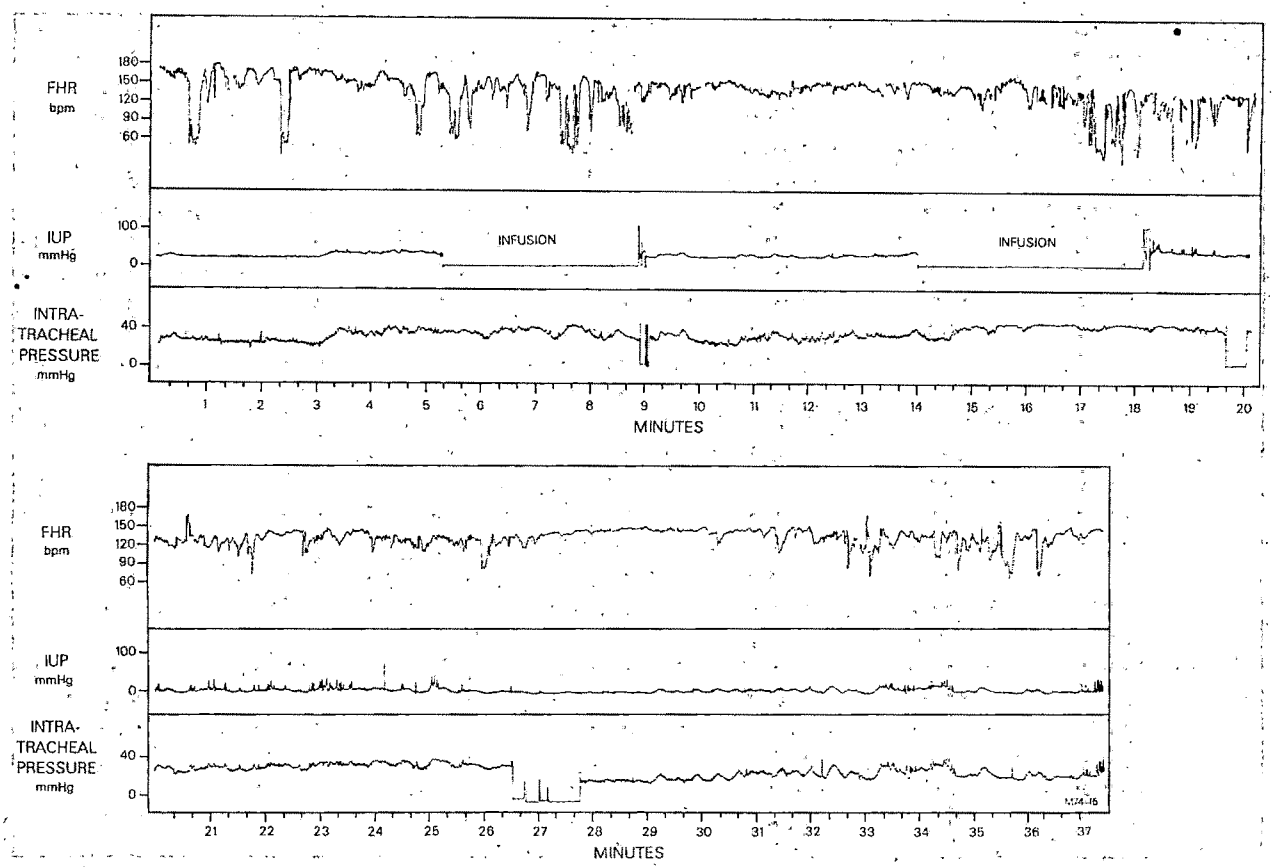


Fig. 1. Variable decelerations are first seen after escape of amniotic fluid. Infusion of 35 c.c. of normal saline initially increases variable decelerations, probably as a result of direct stimulation of the umbilical cord. Restoration of amniotic fluid volume ultimately eliminates the variable decelerations. A second infusion of 40 c.c. continues to relieve cord compression patterns. At the end of the record, variable decelerations recur due to persistent leakage of amniotic fluid.

turbs the normal balance of pressure received by the uterine contents during uterine contractions and facilitates occlusion of the umbilical vessels. With intact membranes, a rise in amniotic fluid pressure will be compensated for by a similar rise in pressure of fetal blood inside the umbilical vessels. After amniotomy, the cord may be trapped between the uterus and fetus and more easily occluded during contractions. Early artificial rupture of membranes has been associated with an increased incidence of Type I dips and a lower mean umbilical artery pH at delivery.

Transient fetal acidosis has also been documented at the time of amniotomy.[7] Brotanek and Hodr[8] attribute this change to a decrease in uterine blood flow. Kubli[9] suggests that this acidosis, which is often associated with FHR changes indicating prolonged cord compression, results from a transient disturbance of umbilical circulation. Our experience with the fetal rhesus monkey preparation would support Kubli's clinical observations.

Early investigations by Barcroft[10] and subsequent studies by Hon[11] and others have confirmed the relationship between umbilical cord occlusion and variable decelerations. Working with an exteriorized fetal goat preparation, Barcroft[10] demonstrated an abrupt fall in heart rate after complete cord occlusion. Bilateral vagotomy eliminated this rapid deceleration. Hon[12] documented a similar nonuniform periodic change in the human FHR after cord prolapse between the fetal thighs. He[13] believes it reasonable to assume that variable deceleration present in utero is caused by cord compression. Recently, Goldkrand[14] observed that 82 per cent of fetuses with abnormal cord position demonstrated FHR patterns consistent with cord occlusion.

Our experimental data indicate that amniotic fluid volume may be a critical factor in protection of the cord. We have demonstrated an association between acute reduction of fluid and variable decelerations. If amniotomy is performed, the clinician may expect variable decelerations in labor.

REFERENCES

1. Hon, E. H.: An Atlas of Fetal Heart Rate Patterns, New Haven, 1968, Harty Press.
2. Martin, C. B., Jr., Murata, Y., and Parer, J. T.: A method for obtaining biochemical and biophysical measurements from rhesus monkey fetuses for prolonged periods, AM. J. OBSTET. GYNECOL. **117:** 126, 1973.
3. Ostergard, D. R.: The physiology and clinical importance of amniotic fluid. A review, Obstet. Gynecol. Survey **25:** 297, 1970.
4. Freeman, R. K., and James, J.: Clinical experience with the oxytocin challenge test: II. An ominous atypical pattern. Obstet. Gynecol. **46:** 255, 1975.
5. Caldeyro-Barcia, R., Mendez-Bauer, C., Pose, S., and Poseiro, J. J.: Fetal monitoring in labor, *in* Wallace, H. M., Gold, E. M., and Lis, E. F., editors: Maternal and Child Health Practices. Problems, Resources, and Methods of Delivery, Springfield, Illinois, 1973, Charles C Thomas, Publisher, p. 332.
6. Caldeyro-Barcia, R., Schwarz, R., Belizán, J. M., Martell, M., Nieto, F., Sabatino, H., and Tenzer, S. M.: Adverse perinatal effects of early amniotomy during labor, *in* Gluck, L., editor: Modern Perinatal Medicine,, Chicago, 1974, Year Book Medical Publishers, Inc., p. 431.
7. Lumley, J., and Wood, C.: Transient fetal acidosis and artificial rupture of the membranes, Aust. N. Z. J. Obstet. Gynaecol. **11:** 221, 1971.
8. Brotanek, V., and Hodr, J.: Fetal distress after artificial rupture of membranes, AM. J. OBSTET. GYNECOL. **101:** 542, 1968.
9. Kubli, F. W.: Influence of labor on fetal acid-base balance, Clin. Obstet. Gynecol. **11:** 168, 1968.
10. Barcroft, J.: Research on prenatal life, Springfield, Illinois, 1947, Charles C Thomas, Publisher.
11. Hon, E. H.: Observations on "pathologic" fetal bradycardia, AM. J. OBSTET. GYNECOL. **77:** 1084, 1959.
12. Hon, E. H.: The fetal heart rate patterns preceding death in utero, AM. J. OBSTET. GYNECOL. **78:** 47, 1959.
13. Hon, E. H.: Additional observations on "pathologic" bradycardia, AM. J. OBSTET. GYNECOL. **118:** 428, 1974.
14. Goldkrand, J. W., and Speichringer, J. P.: "Mixed cord compression," fetal heart rate pattern, and its relation to abnormal cord position, AM. J. OBSTET. GYNECOL. **122:** 144, 1975.

Incorporation of ^{14}C-1-palmitate into rabbit fetal lipids in vivo

J. J. BIEZENSKI, M.D.

Chicago, Illinois

^{14}C-1-palmitate was injected into rabbit fetuses in utero. Fetal liver, blood, carcass, and placenta collected after 15, 60, 180, and 360 minutes were analyzed for radioactivity in lipid classes. Incorporation differed with tissue and lipid. Highest total early specific activity was detected in plasma but later liver displayed the most extensive incorporation. Phospholipid incorporation was more rapid in all tissues than that of other glycerides. Plasma triglycerides did not display any radioactivity for 3 hours. Results point to multicentric origin of plasma lipids. Ready utilization of the palmitate indicates that maternal fatty acid transfer plays an important role in fetal lipid homeostasis.

THERE ARE three possible sources of fetal lipids: transfer from the mother, placental synthesis, and fetal lipogenesis. Transplacental passage of maternal unesterified fatty acids has been documented both in vivo[1] and in perfusion experiments.[2] Esterified fatty acids in any form, that is, as triglycerides,[3] phosphoglycerides,[4, 5] or sterol esters,[6] are not transferred directly across the placenta. Biezenski and associates[7] showed that placental contribution may take the form of an "indirect" transfer characterized by partial placental hydrolysis of phospholipids absorbed from maternal plasma followed by secretion of resynthesized phospholipids into the umbilical vein. There is no evidence that placenta synthesizes lipids for the fetus de novo, though it does display a high lipogenic ability.[8] Fetal fatty acid synthesis by various organs has been amply demonstrated both in vivo[9] and in tissue slices.[10] Precursors used included tritiated water, acetate, citrate, pyruvate, and glucose.

Fetal liver at term displays a well-developed extramitochondrial enzyme system for fatty acid and sterol formation.[11] The synthesis starts with acetyl Co-A produced by the direct oxydative pathway of the hexose monophosphate shunt (HMS) and by the glycolytic pathway of Embden-Meyerhof. Nicotinamide adenine dinucleotide phosphate (NDAPH) required during the synthesis is produced by HMS. Acetyl Co-A is converted to malonyl Co-A with the help of co-carboxylase, which displays low activity in early gestation and may be rate-limiting. The fatty acid synthesized is mainly palmitic. Alpha-glycerophosphate, which is the essential initial substrate in glyceride and phosphoglyceride synthesis, is also produced by the Embden-Meyerhof pathway. The next step in the synthesis consists of acylation of α-glycerophosphate to phosphatidic acid. Ready formation of this phospholipid even in early gestation indicates abundance of fatty acid transferases which catalyse the acylation. However, formation of α-glycerophosphate may be rate-limiting.

This report traces the fate of intrafetally injected palmitic acid. The purpose was to bypass the possible rate-limiting reactions in the fatty acid synthesis. It is presumed that the disposition of the injected acid will have the same characteristics as if the acid were derived from the mother or through fetal synthesis.

Materials and methods

Nonfasting white New Zealand rabbits at term (28 to 30 days) were anesthetized with pentobarbital[5] and subjected to a laparotomy. Fetal parts were ascertained by palpation and each fetus was injected intraperitoneally through the uterus with 37.5 μc of sodium ^{14}C-1-

From the Department of Obstetrics and Gynecology, The Abraham Lincoln School of Medicine, University of Illinois at the Medical Center.

This study was supported by Grant No. HD 00441 from the Institute of Human Growth and Development, National Institutes of Health, United States Public Health Service, and by Research Grant Award No. GL535 from the University of Illinois College of Medicine.

Received for publication February 4, 1976.

Accepted April 6, 1976.

Reprint requests: J. J. Biezenski, M.D., Department of Obstetrics and Gynecology, 840 S. Wood St., Chicago, Illinois 60680.

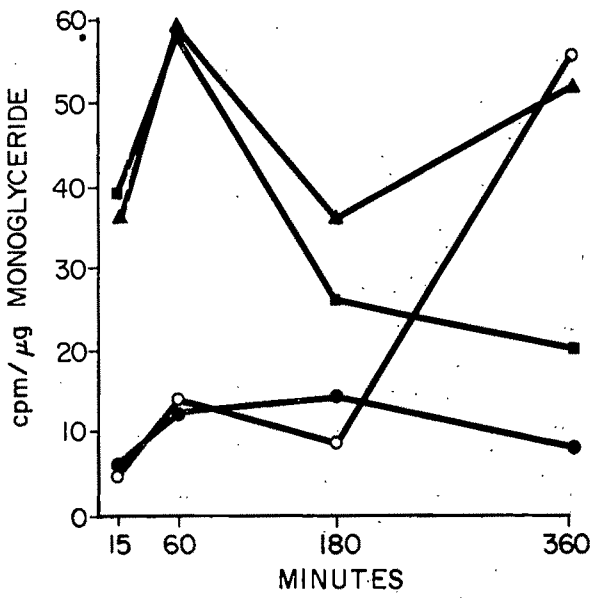


Fig. 1. Specific radioactivity of monoglycerides in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ▪ = plasma, ▲ = carcass.

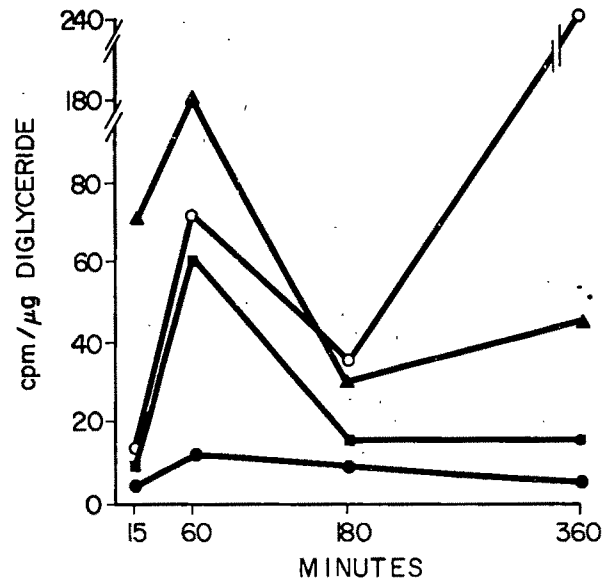


Fig. 2. Specific radioactivity of diglycerides in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ▪ = plasma, ▲ = carcass.

palmitate (40×10^6 c.p.m.) in 0.187 ml. Radioactive sodium palmitate was prepared as follows: palmitic acid-1-^{14}C obtained from New England Nuclear Corporation in 99 per cent purity (by chromatography) was dissolved in hot ethyl alcohol, saponified with 0.05N NaOH, and neutralized with 1N HCl until clear. Fetuses were removed by hysterotomy after 15, 60, 180, or 360 minutes. Except in the 15 minute group the abdominal wall was closed and the rabbit was allowed to wake up. A total of 26 fetuses were removed from seven does. Each uterus was emptied entirely at the same time. Fetal tissues collected included placenta, umbilical vein blood (which was pooled), fetal blood from the heart or neck, fetal liver, and fetal carcass. Tissues were weighed, placed in chloroform : methanol, 2 : 1 (v/v), and kept at −20° C. until extraction. Plasma was obtained by centrifugation of ethylene diamine tetra-acetic acid (EDTA) containing blood. Lipid extraction and purification were carried out as described before.[5, 7] Lipid classes were separated by thin-layer chromatography, identified, and eluted quantitatively from scraped-off spots.[7] Recovery of applied lipids was close to 100 per cent. Total radioactivity recovered from each fetus was 50 to 75 per cent of the amount injected. Lipid quantitation and radioactivity assays were done as before.[7] Reagents were of analytical grade but not redistilled. Radioactivity is reported as true specific activity (TSA) in counts per minute per gram of tissue (milliliters of plasma). Relative specific activity (RSA) of each lipid class is expressed as the ratio of percentage of lipid radioactivity to the percentage of lipid mass that the class represented.

Table I. Specific radioactivity of tissue lipids

	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Plasma	50 ± 18†	109 ± 24	173 ± 39	99 ± 24
Placenta	32 ± 17	78 ± 13	133 ± 43	87 ± 15
Liver	52 ± 20	195 ± 41	311 ± 53	2,440 ± 615
Carcass	414 ± 66	1,198 ± 252	414 ± 87	541 ± 77

*Time after injection.
†Cpm/Gm.(ml.) × 10^{-3} ± S.E.M.

Results

Total tissue radioactivity. After 15 minutes, carcass displayed much higher radioactivity than the other tissues (Table I). However, after 6 hours, placenta, liver, and plasma radioactivity increased two to four times, whereas carcass radioactivity remained the same. Most of this increase occurred after 3 hours. Most of the early counts were in unesterified fatty acids and a detailed lipid radioactivity analysis was essential.

Fetal plasma. An interesting finding was high immediate cholesterol specific activity and a very low triglyceride radioactivity (Table II). In fact, very little radioactivity was seen in triglycerides until 3 hour samples. With time TSA of all esterified compounds increased but only in triglycerides did the RSA (Table III) show a great increment. The percentage of

Table II. True specific activity in plasma lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	4.0 ± 1.2† (8.0)	13.6 ± 2.5 (11.1)	2.7 ± 0.3 (1.5)	2.0 ± 0.3 (2.0)
Diglycerides	4.1 ± 1.5 (8.2)	28.0 ± 15.3 (22.7)	7.2 ± 1.7 (4.2)	7.0 ± 1.8 (7.1)
Triglycerides	0.08 ± 0.03 (0.2)	1.9 ± 1.0 (1.5)	88.7 ± 27.5 (51.0)	50.4 ± 14.5 (50.7)
Free fatty acids	29.7 ± 11.9 (59.9)	53.6 ± 12.8 (43.6)	36.3 ± 13.7 (21.0)	10.3 ± 2.0 (10.4)
Cholesterol	5.0 ± 0.9 (10.0)	5.8 ± 1.2 (4.7)	3.2 ± 0.7 (1.8)	2.2 ± 0.4 (2.2)
Cholesterol ester	0.1 ± 0.07 (0.2)	0.4 ± 0.05 (0.3)	6.9 ± 1.0 (4.0)	6.5 ± 1.5 (6.5)
Phospholipids	6.6 ± 2.7 (13.5)	19.7 ± 5.3 (16.1)	28.6 ± 2.4 (16.5)	20.9 ± 6.4 (21.1)
Total	49.6	122.9	173.5	99.2

*Time after injection.
†Cpm/ml. × 10^{-3} ± S.E.M. Percentages of radioactivity in parentheses.

Table III. Relative specific activity in plasma lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	6.15†	8.53	1.15	1.53
Diglycerides	1.35	3.78	0.70	1.18
Triglycerides	0.09	0.07	2.42	2.41
Free fatty acids	6.65	4.58	2.21	1.09
Cholesterol	0.76	0.36	0.13	0.16
Cholesterol esters	0.006	0.009	0.13	0.21
Phospholipids	0.70	0.84	0.86	1.10

*Time after injection.
†RSA = $\frac{\text{per cent radioactivity}}{\text{per cent mass}}$

Table IV. True specific activity in umbilical vein plasma lipids

	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	0.0† (0.0)	2.92 (9.9)	2.29 (4.3)	1.69 (3.5)
Diglycerides	0.05 (8.6)	2.10 (7.1)	10.58 (20.0)	5.55 (11.5)
Triglycerides	0.02 (3.5)	2.77 (9.4)	5.44 (10.2)	21.44 (44.4)
Free fatty acids	0.26 (44.7)	13.86 (47.0)	22.16 (41.7)	8.60 (17.8)
Cholesterol	0.15 (26.0)	0.89 (3.0)	4.00 (7.5)	2.00 (4.1)
Cholesterol esters	0.01 (1.7)	0.03 (0.1)	0.06 (0.1)	3.67 (7.6)
Phospholipids	0.09 (15.5)	6.93 (23.5)	8.56 (16.2)	5.25 (11.1)
Total	0.58	29.51	53.15	48.30

*Time after injection.
†Cpm/ml. × 10^{-3}. Per cent of radioactivity in parentheses.

radioactivity found in phospholipids increased by 50 per cent, which was reflected in the RSA.

Umbilical vein plasma. Almost no radioactivity was detected in early samples (Table IV). In time, radioactivity was found in various glycerides but it never reached the values found in fetal plasma.

Placenta. The organ absorbed injected fatty acids slowly and to a lesser degree than plasma (Tables V and VI). More esterification of triglycerides and less of phospholipids was evident in early samples. Both reached a maximum in 3 hours. In general, relative triglyceride acylation was much more extensive, due perhaps to low placental triglyceride level. Fatty acid turnover was rapid as indicated by rapid fall in RSA.

Liver. A somewhat different picture (Tables VII and VIII) was obtained from that in the placenta or plasma. Though relatively highest initial TSA was found in triglycerides the actual counts were low. Marked increase in TSA of all compounds was not evident until 6 hours. Triglycerides showed the largest increment. However, RSA of many lipids remained fairly stable, indicating proportional incorporation. Fatty acid and cholesterol RSA decreased with time.

Carcass. Considerable ester synthesis was immediately evident in all classes but subsequent relative increase in acylation was only three- to five-fold (Tables IX and X). Neither phospholipids nor cholesterol esters reached RSA of 1.0 whereas all glycerides showed proportionality between mass (Table XI) and radioactivity.

Lipids. Partial glycerides (Figs. 1 and 2) reached an early relatively high level of radioactivity in most tissues. With the exception of liver the radioactivity did

Table V. True specific activity in placental lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	2.9 ± 1.7† (11.8)	3.0 ± 1.1 (3.9)	3.3 ± 0.5 (2.0)	1.9 ± 0.3 (2.2)
Diglycerides	2.6 ± 1.3 (10.6)	7.5 ± 3.0 (9.7)	5.1 ± 1.8 (3.0)	2.9 ± 0.5 (3.3)
Triglycerides	3.8 ± 2.6 (15.3)	14.3 ± 4.2 (18.4)	54.0 ± 14.1 (32.7)	26.4 ± 3.5 (30.1)
Free fatty acids	10.3 ± 5.0 (41.8)	35.1 ± 5.0 (44.9)	13.8 ± 2.4 (8.4)	5.3 ± 0.9 (6.1)
Cholesterol	1.6 ± 0.4 (6.4)	2.2 ± 0.5 (2.9)	1.1 ± 0.2 (0.7)	0.9 ± 0.1 (1.1)
Cholesterol esters	0.2 ± 0.1 (0.9)	3.0 ± 1.6 (3.8)	4.6 ± 1.1 (2.8)	2.6 ± 0.8 (3.0)
Phospholipids	9.2 ± 6.4 (13.2)	12.8 ± 4.9 (16.4)	83.2 ± 25.9 (50.4)	47.6 ± 11.1 (54.2)
Total	24.7	78.1	165.3	87.7

*Time after injection.
†Cpm/Gm. × 10^{-3} ± S.E.M. Percentages of radioactivity in parentheses.

Table VI. Relative specific activity in placental lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	5.28†	2.71	1.57	1.64
Diglycerides	2.62	2.45	0.88	0.82
Triglycerides	1.11	1.76	3.64	3.42
Free fatty acids	8.92	10.38	2.23	1.50
Cholesterol	1.25	0.38	0.10	0.13
Cholesterol esters	0.11	0.38	0.38	0.22
Phospholipids	0.37	0.33	0.73	0.83

*Time after injection.
†$\text{RSA} = \frac{\text{per cent radioactivity}}{\text{per cent mass}}$

not increase or it decreased. Esterification of triglycerides (Fig. 3), phospholipids (Fig. 4), and cholesterol esters (Fig. 5) increased with time, but differences between tissues and the lipid classes were evident. Phospholipids of all tissues displayed the most rapid incorporation, cholesterol esters the lowest, whereas triglyceride incorporation depended on the tissue at all points in time. Plasma phospholipid TSA was higher or equal to that found in other tissues until 6 hours were reached. By contrast, plasma triglyceride TSA was initially very much lower than in other tissues and it did not reach their levels for 3 hours. The rapid appearance of radioactivity in unesterified cholesterol (Fig. 6) was noted in all tissues except liver. Decreasing free fatty acid TSA (Fig. 7) was to be expected, though relatively slow initial liver uptake should be emphasized.

Comment

There are several metabolic pathways in which the injected palmitate can be involved. One pathway is breakdown to two carbon units through beta oxidation. This is an important process in the adult to provide energy. Fetal tissues in vitro are capable of palmitic acid utilization for that purpose,[12] but the process was not documented in vivo. Normal fetal respiratory quotient is less than 1.0, indicating glucose combustion rather than fat utilization. Other ways in which palmitate can be involved are transformation into higher fatty acids other than essential by elongation and desaturation, and activation with Co-A to form palmityl Co-A as an intermediate in cholesterol synthesis. Present results indicate rapid availability and abundance of the coenzyme and of other enzymes involved in cholesterol synthesis. Acetyl Co-A, which is also a starting point in sterol synthesis, can be obtained through glycolysis or through beta oxidation, which might have been the case in our experiments. Incorporation into glycerides and phosphoglycerides appeared to be the principal pathway of palmitate disposition. High early specific activity of monoglycerides and diglycerides, intermediates in phospholipid and tri-

Table VII. True specific activity in liver lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	0.8 ± 0.2† (1.6)	2.7 ± 0.9 (1.3)	1.6 ± 0.4 (0.5)	10.5 ± 3.2 (0.4)
Diglycerides	3.2 ± 0.8 (6.2)	18.6 ± 7.4 (9.2)	8.7 ± 2.3 (2.8)	62.2 ± 18.1 (2.5)
Triglycerides	18.2 ± 7.8 (35.1)	96.4 ± 34.4 (47.5)	213.5 ± 28.3 (68.6)	11630.4 ± 346.0 (67.0)
Free fatty acids	22.5 ± 9.8 (43.5)	46.0 ± 12.4 (22.8)	45.0 ± 15.7 (14.4)	451.0 ± 188.4 (18.5)
Cholesterol	1.4 ± 0.4 (2.8)	9.3 ± 2.6 (4.6)	2.7 ± 0.5 (0.9)	17.9 ± 4.7 (0.7)
Cholesterol esters	0.3 ± 0.1 (0.5)	3.0 ± 1.3 (1.5)	2.6 ± 0.2 (0.9)	20.7 ± 5.9 (0.8)
Phospholipids	5.3 ± 1.3 (10.3)	26.5 ± 5.8 (13.1)	37.1 ± 12.0 (11.9)	247.1 ± 71.4 (10.1)
Total	51.7	202.7	311.3	247.1

*Time after injection.
†Cpm/Gm. × 10^{-3} ± S.E.M. Percentages in parentheses.

Table VIII. Relative specific activity in liver lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	2.00†	1.60	0.50	0.40
Diglycerides	2.20	5.66	1.86	1.86
Triglycerides	1.27	1.66	2.74	2.78
Free fatty acids	10.30	7.15	3.48	3.76
Cholesterol	1.94	2.42	0.47	0.47
Cholesterol esters	0.11	0.31	0.20	0.26
Phospholipids	0.21	0.22	0.18	0.14

*Time after injection.
†$RSA = \frac{\text{per cent radioactivity}}{\text{per cent mass}}$

Table IX. True specific activity in carcass lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	5 ± 1† (1.3)	24 ± 4 (2.0)	5 ± 0.7 (1.3)	8 ± 2 (1.4)
Diglycerides	41 ± 7 (9.9)	105 ± 41 (8.7)	16 ± 5 (3.9)	25 ± 5 (4.6)
Triglycerides	38 ± 17 (9.3)	156 ± 60 (13.0)	206 ± 42 (49.8)	195 ± 19 (36.0)
Free fatty acids	285 ± 67 (69.1)	765 ± 171 (64.0)	46 ± 9 (11.1)	154 ± 43 (28.4)
Cholesterol	15 ± 2 (3.5)	44 ± 7 (3.7)	5 ± 3 (1.3)	5 ± 1 (0.9)
Cholesterol esters	1.2 ± 0.2 (0.3)	9 ± 3 (0.8)	2.3 ± 0.6 (0.6)	3.7 ± 0.5 (0.7)
Phospholipids	27 ± 8 (6.6)	94 ± 42 (7.8)	132 ± 30 (32.0)	151 ± 25 (28.0)
Total	413	1,197	414	541

*Time after injection.
†Cpm/Gm. × 10^{-3} ± S.E.M. Per cent of radioactivity in parentheses.

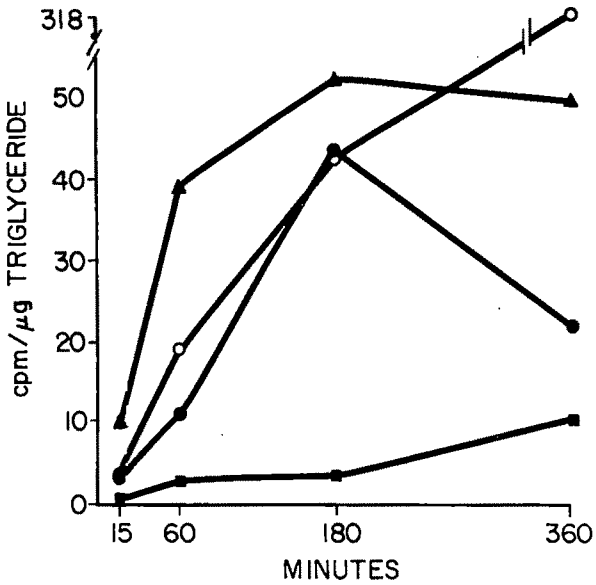


Fig. 3. Specific radioactivity of triglycerides in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ■ = plasma, ▲ = carcass.

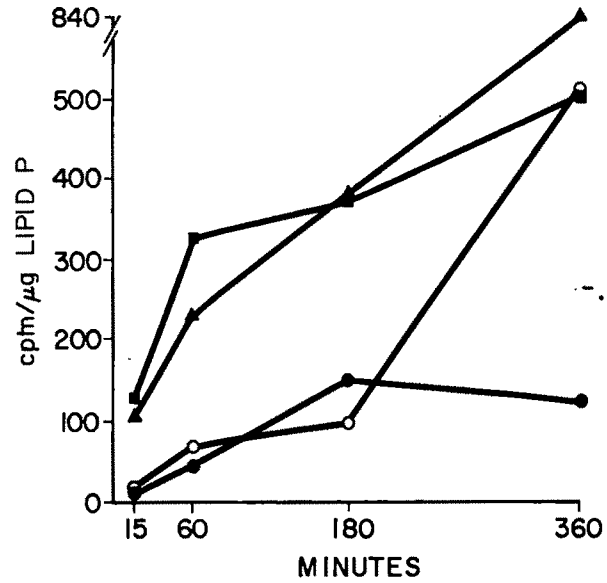


Fig. 4. Specific radioactivity of phospholipids in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ■ = plasma, ▲ = carcass.

glyceride synthesis, pointed to ready availability of α-glycerophosphate, phosphatidic acid transferase, and acyl transferases. Rapid phospholipid formation also pointed to the abundance of the cytidine diphosphate transferase systems, particularly CDP-choline. Esterification of carcass triglycerides was evident in early samples which reflected extensive adipose tissue deposition. The fat content of newborn rabbits amounts to about 2 per cent, nearly all of which is deposited in the last few days of gestation.

Studies on fetal lipogenesis indicate high synthetic potential. Fain and Scow[9] concluded that in the rat fetal lipogenesis could account for all the triglyceride found at term. Similarly, Goldwater and Stetten[13] calculated that only 1.5 per cent of newborn fatty acids derived from the mother. By contrast, Van Duyne and associates[1] concluded that placental fatty acid transfer from the mother to the fetus in the rabbit was sufficient to account for all the fatty acids found at birth. The finding was confirmed in the monkey[14] but not in the sheep.

Conclusions regarding extent of placental transfer must take into account not only the species of animal but also the fatty acid itself. In the guinea pig, the rate of transfer of linoleic acid, an essential fatty acid, was double that of palmitic acid.[16]

Introduction of a fatty acid into the circulation of an adult animal results in rapid absorption and incorporation of the label into lipids. The injected palmitate appeared rapidly in the fetal circulation but significant

Table X. Relative specific activity in carcass lipids

Lipid class	*15 min.**	*60 min.*	*180 min.*	*360 min.*
Monoglycerides	1.08†	2.00	1.16	1.25
Diglycerides	2.09	1.88	0.79	1.09
Triglycerides	0.32	0.43	1.69	1.39
Free fatty acids	9.52	8.83	1.59	3.04
Cholesterol	0.56	0.65	0.14	0.11
Cholesterol esters	0.13	0.36	0.27	0.36
Phospholipids	0.14	0.15	0.65	0.54

*Time after injection.

†RSA = $\frac{\text{per cent radioactivity}}{\text{per cent mass}}$

liver pickup or incorporation into lipid classes did not occur for several hours. Furthermore, the incorporation paralleled the rate of absorption from plasma, which indicated that esterification of liver glycerides was dependent partly upon the fatty acid which originated outside the liver (e.g., from the mother). In agreement with our previous findings,[17] the results de-emphasize the role of the fetal liver in lipid homeostasis. They also underscore the importance of placental fatty acid transfer.

One of the principal objects of the experiments was to obtain information regarding the source of fetal plasma lipids. In the adult, all plasma lipids are synthesized by the liver and released into plasma in the form of lipoproteins. Our previous experiments strongly suggested that fetal liver was not the source of fetal plasma phospholipids.[17] From other experiments we

Table XI. Lipid content of fetal tissues

Lipid class	*Plasma**	*Liver*	*Placenta*	*Carcass*
Monoglycerides	0.10 ± 0.01† (1.3)	0.15 ± 0.03 (0.8)	0.25 ± 0.17 (1.4)	0.15 ± 0.02 (1.2)
Diglycerides	0.47 ± 0.04 (6.0)	0.26 ± 0.17 (1.3)	0.64 ± 0.37 (4.0)	0.57 ± 0.13 (4.4)
Triglycerides	1.64 ± 0.12 (21.0)	5.13 ± 1.39 (25.2)	1.25 ± 0.10 (2.3)	3.97 ± 1.08 (31.0)
Free fatty acids	0.74 ± 0.05 (9.5)	0.73 ± 0.14 (5.5)	0.67 ± 0.26 (3.7)	0.83 ± 0.09 (5.8)
Cholesterol	1.02 ± 0.06 (13.0)	0.34 ± 0.08 (1.6)	1.35 ± 0.58 (16.5)	0.85 ± 0.17 (6.7)
Cholesterol esters	2.35 ± 0.14 (30.1)	0.81 ± 0.18 (3.6)	1.17 ± 0.37 (6.3)	0.27 ± 0.04 (2.2)
Phospholipids	1.50 ± 0.12 (19.1)	12.15 ± 0.70 (62.0)	10.25 ± 0.70 (65.8)	6.29 ± 0.22 (48.7)
Total	7.83	19.57	15.57	12.93

*μg/ml. (Gm.) ± S.E.M.
†Per cent of lipid.

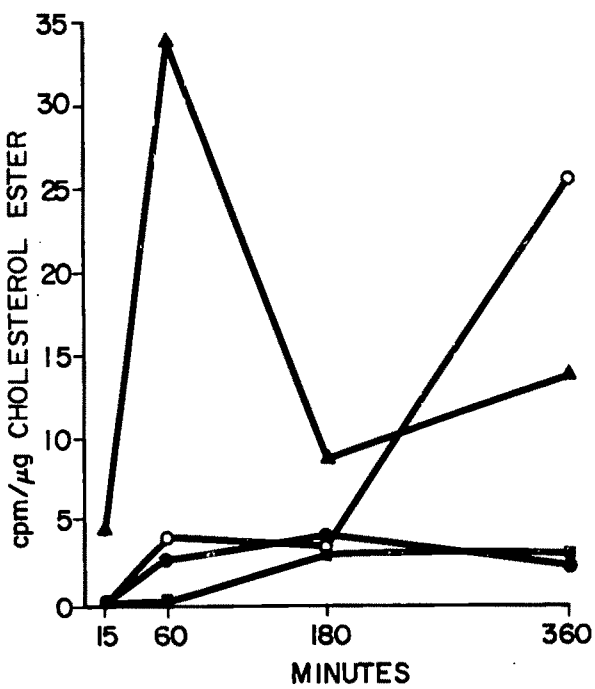


Fig. 5. Specific radioactivity of cholesterol esters in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ▪ C= plasma, ▲ = carcass.

concluded that placenta was the source of fetal plasma phospholipids,[7] but not necessarily so of other lipids. Phospholipids labeled with ^{32}P and ^{14}C fatty acid (palmitic or oleic) were injected into maternal rabbits. Thirty minutes later ^{14}C radioactivity was found in all lipid classes (except cholesterol esters) of umbilical vein plasma and fetal plasma, although most radioactivity was found in unesterified fatty acids. Specific activity of umbilical vein plasma lipids was much higher than that of general fetal circulation plasma lipids. In the present series plasma phospholipid specific activity was high, even in early specimens. Very low phospholipid radioactivity in umbilical vein plasma excluded placenta as the possible source of those phospholipids. Lower phospholipid specific activity in either carcass or liver similarly apparently excluded those tissues from such consideration because the precursor-product relationship was not obtained. Since after incorporation most radioactivity was still present in the palmitic acid, the acid must have entered the phospholipid molecule, bypassing the conventional synthetic process. Theoretically, this can occur in two ways: acylation or exchange. Kyei-Aboagye and associates[18] showed direct palmitic acylation of lysolecithin to lecithin by rabbit lung homogenate after addition of Co-A and ATP to the reaction mixture. Lysolecithin represents 11 per cent of rabbit fetal plasma phospholipids.[19]

The phospholipase reacylation reaction described by Lands[20] may be operative in the fatty acid exchange pathway. Accordingly, a fatty acid within a phospholipid molecule may be exchanged for another fatty acid without disrupting the molecular structure. A similar process has been described for phospholipid P. Presence of suitable enzymes in fetal plasma has not been sought. However, low specific activity of cholesterol esters indicates that another acyl transferase, lecithin-cholesterol transferase, is not abundant in fetal plasma.

Plasma triglycerides did not display much radioactiv

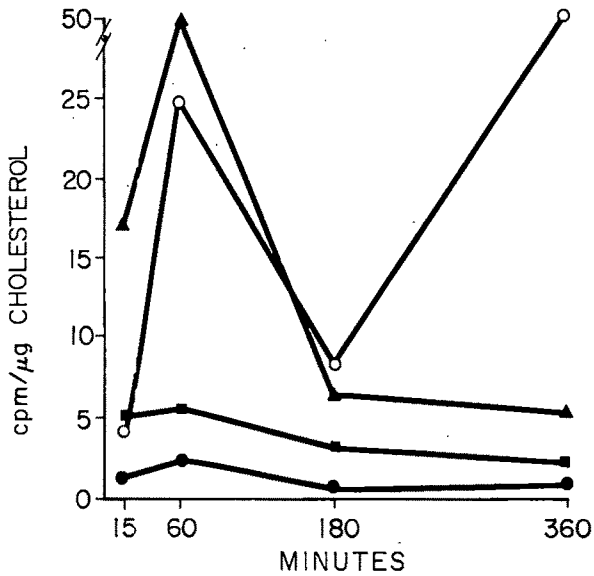


Fig. 6. Specific radioactivity of free cholesterol in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ■ = plasma, ▲ = carcass.

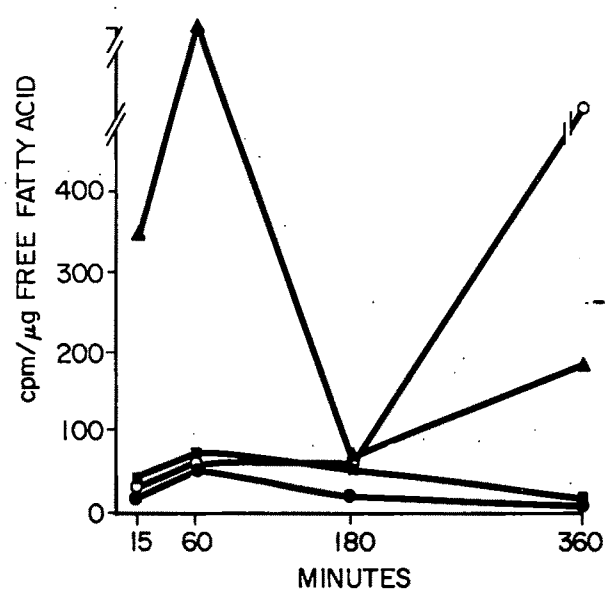


Fig. 7. Specific radioactivity of free fatty acids in fetal tissues after intrafetal injection of ^{14}C-palmitate in utero. • = placenta, o = liver, ■ = plasma, ▲ = carcass.

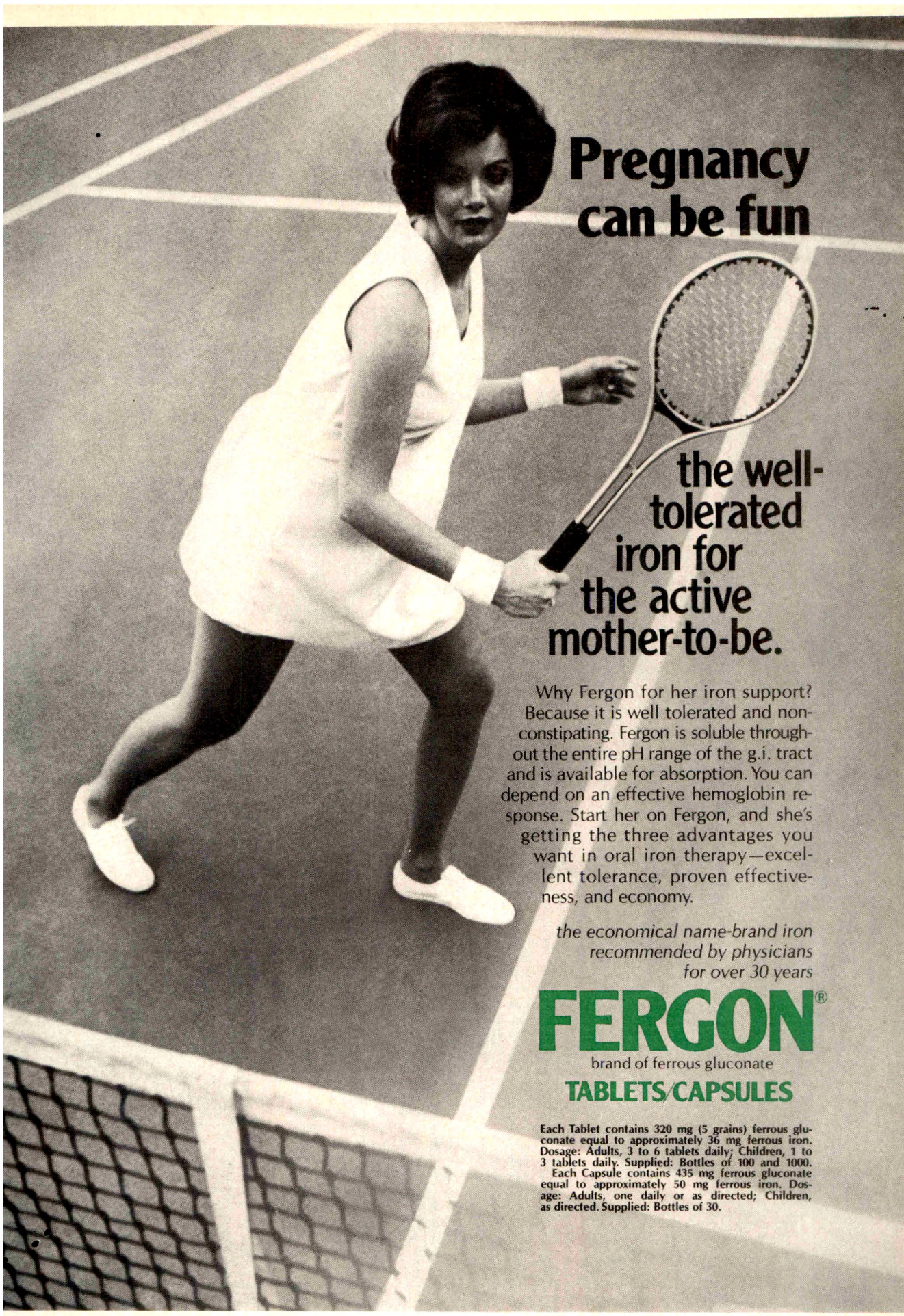
ity for 3 hours. Liver triglyceride specific activity was always higher, which is consistent with the possibility of triglyceride hepatic origin. The triglyceride specific activity never reached the level found in phospholipids, although both classes contain about 30 per cent palmitic acid, which further emphasized the likelihood of a different origin of the two lipid classes.

Fetal lipogenic potential increases as pregnancy progresses. All studies show that close to term placental phospholipid transfer does not take place,[4, 5, 7] though some transfer may occur in very early rabbit gestation. From information obtained from our various experiments and those of others, we conclude that late in gestation fetal lipid homeostasis utilizes both maternal and fetal resources. The two mechanisms are not exclusive and may be complementary, depending on the availability of maternal fatty acids. Since transfer of unesterified fatty acids depends on the concentration gradient on the two sides of the placental membrane, conditions leading to high fatty acid level in maternal plasma are likely to lead to a higher transfer. This could be the reason for increased lypolysis and fatty acid mobilization causing high levels of unesterified fatty acids observed in plasma during pregnancy.[2] Thus, the old hypothesis that maternal hyperlipemia is due to fetal lipid needs might at least be partially confirmed.

REFERENCES

1. Van Duyne, C. M., Havel, R. J., and Felts, J. M.: Cholesterol transfer of palmitic acid-1-C^{14} in rabbits, Am. J. Obstet. Gynecol. **84:** 1069, 1962.
2. Szabo, A. J., Grimaldi, R. D., and Jung, W. F.: Palmitate transport across perfused human placenta, Metabolism **18:** 4061, 1969.
3. McBride, D. W., and Korn, E. D.: Uptake of free fatty acids and chylomicron glycerides by guinea pig mammary gland in pregnancy and lactation, J. Lipid Res. **5:** 453, 1964.
4. Popják, G., and Beeckman, S. M. L.: Are phospholipins transmitted through the placenta? Biochem. J. **46:** 99, 1950.
5. Biezenski, J. J.: Role of placenta in fetal lipid metabolism. I. Injection of phospholipids double labeled with C^{14}-glycerol and P^{32} into pregnant rabbits, Am. J. Obstet. Gynecol. **104:** 1177, 1969.
6. Lopez-Santolino, A., Miller, O. N., and Mulorey, J. E.: Effect of prenatal diet on serum cholesteryl ester fatty acids in newborn and adult rats, Proc. Soc. Exp. Biol. Med. **118:** 829, 1965.
7. Biezenski, J. J., Carrozza, J., and Li, J.: Role of placenta in fetal lipid metabolism. III. Formation of rabbit plasma phospholipids, Biochim. Biophys. Acta **239:** 92, 1971.
8. Szabo, A. J., Grimaldi, D., and Rodolfo de L.: Triglyceride synthesis by the human placenta. I. Incorporation of labeled palmitate into placental triglyceride, Am. J. Obstet. Gynecol. **115:** 257, 1973.
9. Fain, J. N., and Scow, R. O.: Fatty acid synthesis in vivo in maternal and fetal tissues in the rat, Am. J. Physiol. **210:** 19, 1966.
10. Villee, C. A., and Hagerman, D. D.: Effect of oxygen deprivation on the metabolism of fetal and adult tissues, Am. J. Physiol. **194:** 457, 1958.
11. Biezenski, J. J.: Fetal lipid metabolism, *in* Wynn, R. M.,

editor: Obstetrics and Gynecology Annual, New York, 1975, Appleton-Century-Crofts, pp. 39-70.
12. Roux, J. F., and Myers, R. E.: In vitro metabolism of palmitic acid and glucose in the developing tissue of the Rhesus monkey, AM. J. OBSTET. GYNECOL. **118:** 385, 1974.
13. Goldwater, W. H., and Stetten, De W., Jr.: Studies in fetal metabolism, J. Biol. Chem. **169:** 723, 1947.
14. Portman, O. U., Behrman, R. E., and Soltis, P.: Transfer of free fatty acids across the primate placenta, Am. J. Physiol. **216:** 143, 1969.
15. Van Duyne, C. M., Parker, H. R., Havel, R. J., and Holm, L. W.: Free fatty acid metabolism in fetal and newborn sheep, Am. J. Physiol. **199:** 987, 1960.
16. Hershfield, M. S., and Nemeth, A. M.: Placental transport of free palmitic and linoleic acids in the guinea pig, J. Lipid Res. **9:** 460, 1968.
17. Biezenski, J. J., and Kimmel, B.: Inability of fetal liver to synthesize plasma phospholipids, Proc. Soc. Exp. Biol. Med. **130:** 1238, 1969.
18. Kyei-Aboagye, K., Rubenstein, D., and Beck, J. C.: Biosynthesis of dipalmitoyl lecithin by the rabbit lung, Can. J. Biochem. **51:** 1581, 1973.
19. Biezenski, J. J.: Origin of plasma phospholipids, *in* Pecile, A., and Finzi, C., editors: Feto-placental Unit, Amsterdam, 1969, Excerpta Medica Foundation, pp. 221-239.
20. Lands, W. E. M.: Metabolism of glyserolipids. II. Enzymatic acylation of lysolecithin, J. Biol. Chem. **235:** 2233, 1960.
21. Biezenski, J. J.: Maternal lipid metabolism, *in* Wynn, R. M., editor: Obstetrics and Gynecology Annual, New York, 1974, Appleton-Century-Crofts, pp. 203-233.



Pregnancy can be fun

the well-tolerated iron for the active mother-to-be.

Why Fergon for her iron support? Because it is well tolerated and non-constipating. Fergon is soluble throughout the entire pH range of the g.i. tract and is available for absorption. You can depend on an effective hemoglobin response. Start her on Fergon, and she's getting the three advantages you want in oral iron therapy—excellent tolerance, proven effectiveness, and economy.

the economical name-brand iron recommended by physicians for over 30 years

FERGON®

brand of ferrous gluconate

TABLETS/CAPSULES

Each Tablet contains 320 mg (5 grains) ferrous gluconate equal to approximately 36 mg ferrous iron. Dosage: Adults, 3 to 6 tablets daily; Children, 1 to 3 tablets daily. Supplied: Bottles of 100 and 1000.

Each Capsule contains 435 mg ferrous gluconate equal to approximately 50 mg ferrous iron. Dosage: Adults, one daily or as directed; Children, as directed. Supplied: Bottles of 30.

BREON **BREON LABORATORIES INC.,** Subsidiary of Sterling Drug Inc., 90 Park Avenue, New York, N.Y. 10016

Comprehensive Group Health Care Plan

(Winston-Salem, North Carolina)

A new prepaid group health plan (Multi-specialty) opened July, 1976, for employees of R.J. Reynolds Industries, Inc. Assured growth, continuing expansion. The following board-qualified specialists are needed:

INTERNISTS PEDIATRICIANS OB/GYN

This represents an opportunity to practice under ideal conditions in modern new facilities and excellent hospitals. Medical school environment.

Winston-Salem is located in the Piedmont section of North Carolina and is within reasonable driving distances to the Atlantic Ocean and Blue Ridge Mountains. The city is noted for its cultural, recreational, and college environments.

Salary commensurate with experience. Liberal fringe benefits including paid vacation, CME, retirement, life insurance, and health coverage. Malpractice insurance paid. Relocation expenses paid.

Send curriculum vitae, including salary requirements to:

Reid Bahnson, M.D.
Medical Director
W-S HEALTH CARE PLAN, INC.
250 Charlois Blvd.
Winston-Salem, North Carolina 27103

Winston-Salem Health Care Plan Inc.

An Equal Opportunity Employer M/F

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 339, Erie, Pennsylvania 16512.

IN MONILIASIS
BETADINE® Microbicides Vaginitis Regimen

Full Prescribing Information
BETADINE® Vaginal Gel
(povidone-iodine)

BETADINE Vaginal Gel (povidone-iodine) makes available elemental iodine in a form that maintains iodine's microbicidal activity, yet is virtually nonirritating, nontoxic and is nonstaining to skin and natural fabrics.

- Kills trichomonas, monilia, and other iodine-susceptible vaginal organisms responsible for specific and nonspecific vaginal infections.
- Active in the presence of blood, pus, or vaginal secretions.
- Virtually nonirritating to vaginal mucosa.
- Nonstaining to skin, linen or clothing of natural fabrics; color can be washed off with water.

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

Recommended regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution.

Prescribe BETADINE Vaginal Gel (povidone-iodine) as follows: Insert one (1) applicatorful each night, followed the next morning by BETADINE Douche in its therapeutic concentration (2 tablespoonfuls to a quart of lukewarm water).

This regimen is to be followed through the entire menstrual cycle, including the days of menses. If further therapy is warranted, the regimen should be continued through the next two cycles. The patient may be instructed to return for an office visit following two weeks of therapy.

Precaution

If irritation, redness or swelling develop, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

Recommended dosage

One applicatorful (5 Gm.). Each five grams (one applicatorful) is equivalent to fifty milligrams of available iodine.

Supplied

18 Gm. and 3 oz. tubes with applicator.
Only on prescription.

Purdue Frederick

©COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A8201 171276



Lethal to monilia



Gentle to patients

IN MONILIASIS

BETADINE® Microbicides Vaginitis Regimen

High cure rate... rapid symptomatic relief

High cure rate is achieved in monilial vaginitis with the topical regimen employing BETADINE Microbicides:

BETADINE® SOLUTION
BETADINE® VAGINAL GEL*
(povidone-iodine)
BETADINE® DOUCHE

Easy-to-follow regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution which is promptly and decisively microbicidal. Prescribe BETADINE Vaginal Gel (povidone-iodine), one applicatorful of which is to be inserted each night, followed the next morning by BETADINE Douche in therapeutic concentration —2 tablespoonfuls to a quart of luke-warm water.

After 2 weeks

The patient returns for an office visit after two weeks of therapy. In more resistant cases, the regimen may have to be continued through 1 or 2 cycles. BETADINE Microbicides are virtually nonirritating to vaginal mucosa and do not stain skin and natural fabrics.

Lethal to other vaginal pathogens too

The broad-spectrum microbicidal action of BETADINE Microbicides kills not only monilia, but also *Trichomonas* and *Hemophilus vaginalis*.

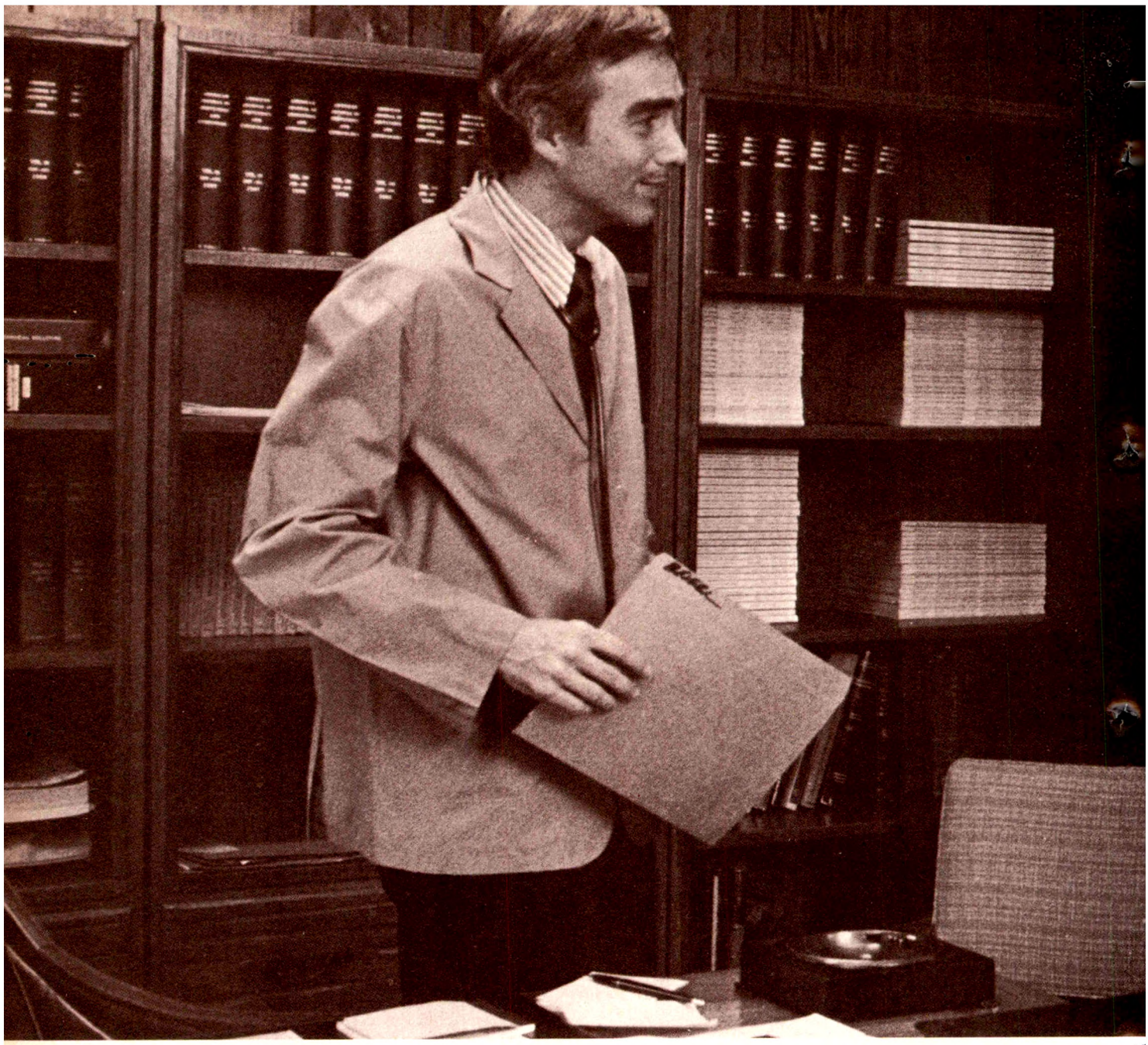
Unlike exclusively antimonilial agents, the BETADINE MICROBICIDES VAGINITIS REGIMEN is not contraindicated when *Trichomonas* or *H. vaginalis* is present.

BETADINE Microbicides kill both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts. Their microbicidal action is maintained in the presence of blood, serum, and vaginal secretions.

*BETADINE Vaginal Gel (povidone-iodine) has been evaluated as possibly effective for use in the management of *Trichomonas vaginalis* vaginitis, monilial vaginitis and nonspecific vaginitis.

Purdue Frederick

See adjoining page for full prescribing information. A8335 178376



Abbott hematinics can help to provide optimum care to term

- These are the only major products containing the exact U.S. RDA* of folic acid for pregnancy—800 mcg.
- Dosage is one-a-day—helps to assure patient cooperation.
- To minimize gastric upset, each product contains 525 mg. of Ferrous Sulfate in controlled-release form—an important consideration in pregnancy.
- Both products contain 500 mg. of Vitamin C to enhance iron absorption.

*Federal Register, 38:20717, Aug. 2, 1973.



Fero-Folic-500® ℞

Controlled-Release Iron
525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption
500 mg. Ascorbic Acid (as sodium ascorbate)

Plus 800 mcg. of Folic Acid

Indications: For the treatment of iron deficiency and prevention of concomitant folic acid deficiency in non-pregnant adults. Also indicated in pregnancy for the prevention and treatment of iron deficiency and to supply a maintenance dosage of folic acid. **Contraindications:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Fero-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

Iberet-Folic-500® ℞

Controlled-Release Iron
525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption
500 mg. Ascorbic Acid (as sodium ascorbate)

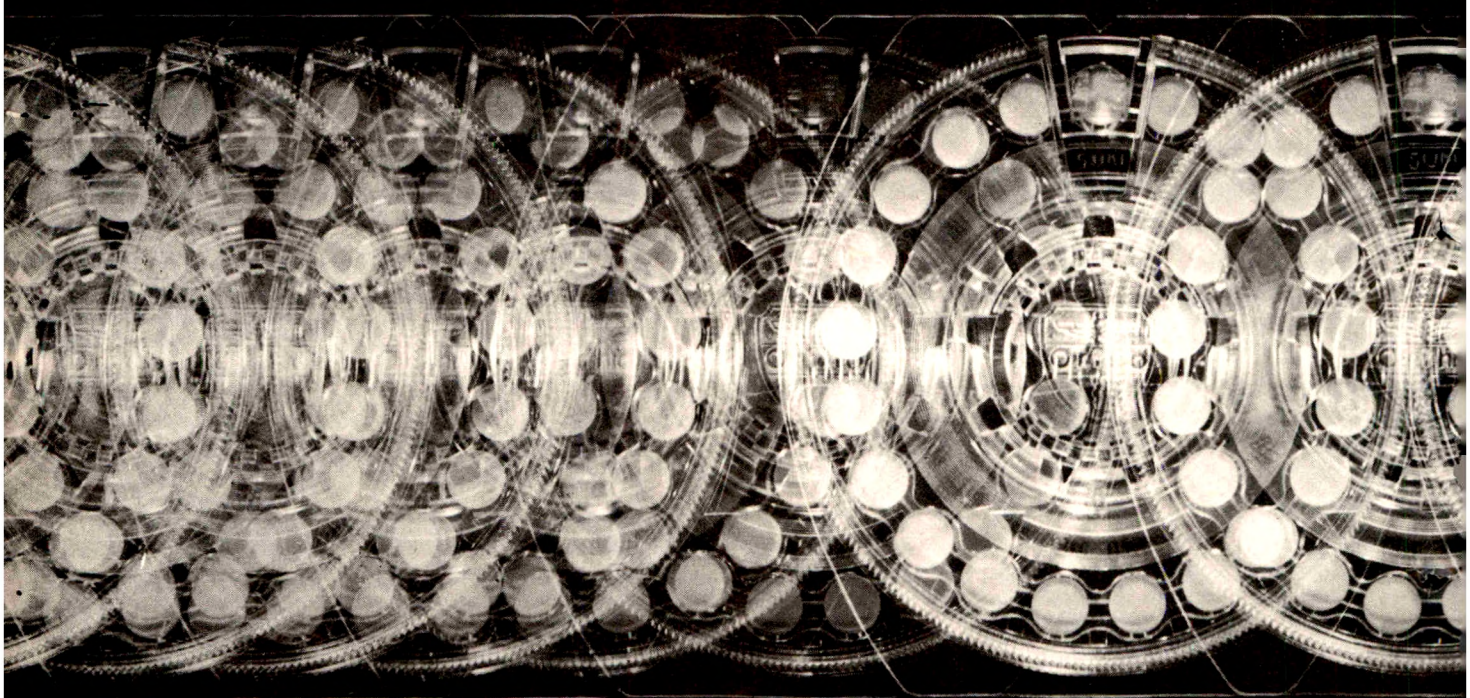
Plus the B-Complex
Niacinamide, 30 mg.; Calcium Pantothenate, 10 mg.; Vitamin B_1 (Thiamine Mononitrate), 6 mg.; Vitamin B_2 (Riboflavin), 6 mg.; Vitamin B_6 (Pyridoxine Hydrochloride), 5 mg.; Vitamin B_{12} (Cyanocobalamin), 25 mcg.

Plus 800 mcg. of Folic Acid

Indications: In non-pregnant adults, for the treatment of iron deficiency and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins. Also indicated in pregnancy for the prevention and treatment of iron deficiency where there is a concomitant deficient intake or increased need for B-complex vitamins (including folic acid). **Contraindication:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Iberet-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. 6033133

ABBOTT

IMPORTANT ANNOUNCEMENT

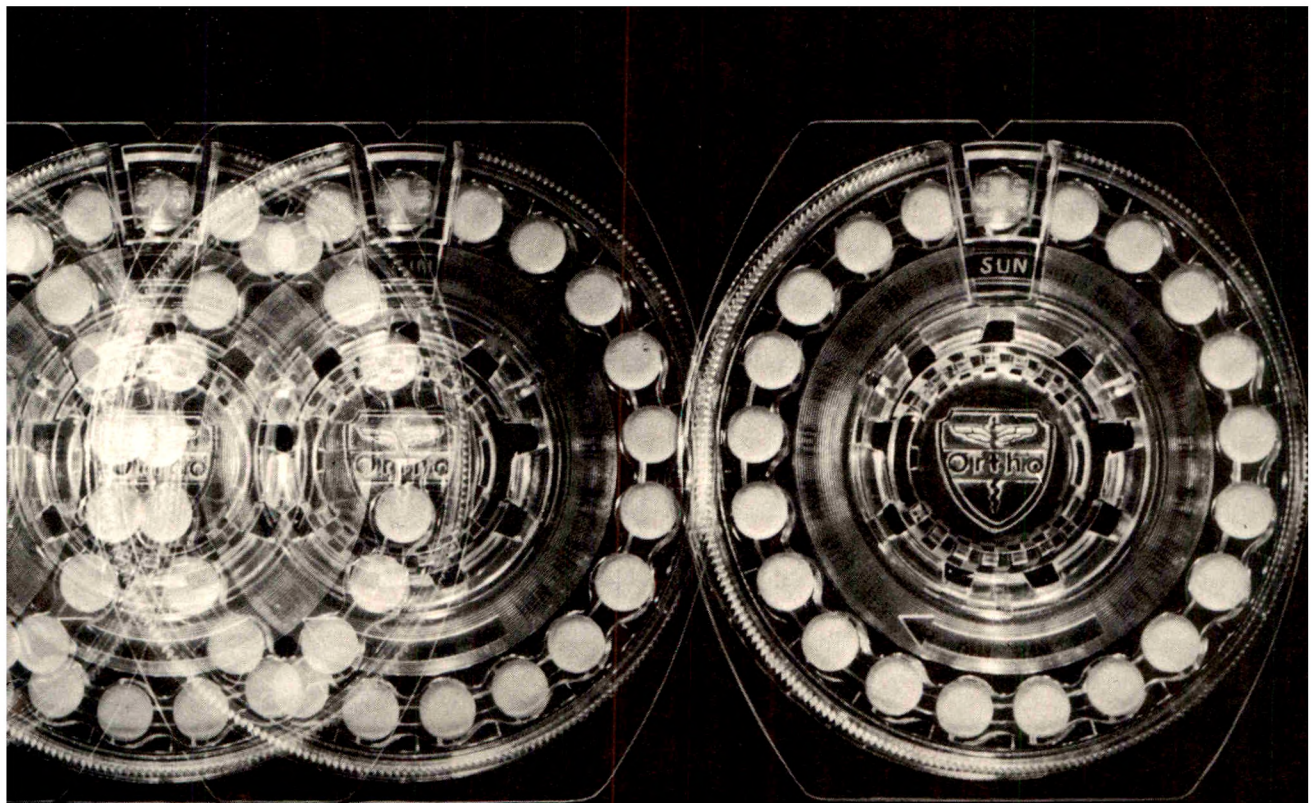


ModiCon

TRADEMARK

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.

to offer lower-dose oral contraception with higher-dose effectiveness†



is back.

Reformulated without dye *ModiCon is back, but without the coloring agent. Quality control testing on new white ModiCon demonstrates excellent stability.*

No change in hormonal content *Alterations in the hormonal content were not necessary. ModiCon still contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.*

Same clinical benefits *ModiCon is back in a new white tablet to offer the same clinically documented benefits as before: low hormonal intake – highly effective – well tolerated‡ – and the only lower-dose combination available in the unique DIALPAK* Tablet Dispenser.*

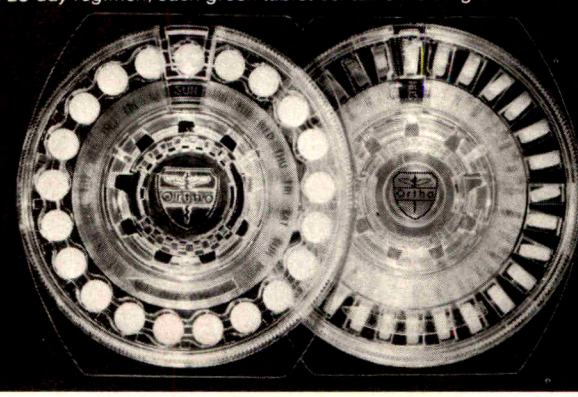
Two regimens *Available in both 21 and 28-day regimens.*

†It should be noted that pregnancy rates are usually derived from studies conducted by different investigators in several population groups and they cannot be compared with precision.

‡Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

ModiCon TRADEMARK is back.

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.



In both 21 and 28-day regimens

Description: Each MODICON Tablet contains 0.5 mg of the progestational substance, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

Each green tablet in the 28-day regimen contains inert ingredients.

Actions: MODICON acts through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of MODICON.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with MODICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of MODICON in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with MODICON. Therefore, if such tests are abnormal in a patient taking MODICON, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged MODICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving MODICON therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with MODICON may mask the onset of the climacteric. 10. The pathologist should be advised of MODICON therapy when relevant specimens are submitted. 11. Susceptible women may experience an *increase in* blood pressure following administration of contraceptive steriods. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, MODICON should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during MODICON therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health: 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.L.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:241-245, May 3, 1975. **12.** Mann, J.L.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J.J.; Nora, A.H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291* (14):697-700, Oct. 3, 1974. 3/7●

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

GYNECOLOGY

The effect of vaginal lubricants on *Neisseria gonorrhoeae*

BALWANT SINGH, PH.D.
JOHN C. CUTLER, M.D.
Pittsburgh, Pennsylvania

The possible interference of vaginal lubricants in culture diagnosis of gonorrhea was investigated by studying in vitro effect of selected lubricants on Neisseria gonorrhoeae. *Two lubricants widely used in family planning and other clinics were demonstrated to have a bactericidal effect on* N. gonorrhoeae *when tested with more than one method. Gonococci were killed on contact with Lubrifoam, even at a 10 per cent concentration, and an exposure time as short as one minute was sufficient to inhibit the growth on chocolate agar medium. The K-Y jelly showed less inhibitory effect than Lubrifoam. These findings suggest that certain vaginal lubricants have bactericidal effects and their presence can inhibit the growth of* Neisseria gonorrhoeae.

GONOCOCCAL INFECTION in a large majority of women does not cause sufficiently marked signs or symptoms to make them aware of the disease and thus report for treatment. Failure to diagnose gonorrhea in women who harbor asymptomatic infection is an important contributing factor in the gonorrhea epidemic. Asymptomatic infected individuals, being unaware, keep spreading the disease. Since the discovery of *N. gonorrhoeae* by Albert Neisser in 1879, numerous techniques have been used to identify gonococci in patients suspected of having gonorrhea; however, the culture technique is a more sensitive method for female patients. The Thayer-Martin (T-M) culture medium, introduced in 1964 and modified in 1966, is a selective medium for culture detection of gonococci.[1] Any clinical laboratory with minimum bacteriologic competency can perform the necessary procedures for isolation and confirmation of *N. gonorrhoeae*. Despite this effective medium for cultural detection and subsequent identification, several investigators have reported conflicting data regarding sensitivity and reproductibility of this culture medium in detecting disease in women.[2] Unfortunately, several conditions and procedures in the course of diagnosis can affect the positive yield. Validity of culture results depends on proper techniques for obtaining, inoculating, and handling specimens. The Venereal Disease Branch, Center for Disease Control, Atlanta, Georgia, has published the recommended criteria and techniques for diagnosis of gonorrhea. The recommendation is that one should use a speculum moistened with warm water without any lubricants for obtaining cervical, urethral, or vaginal cultures. However, some family planning and obstetric-gynecologic clinics prefer to use commercially available lubricants during pelvic examinations.[3] In

From the Graduate School of Public Health, University of Pittsburgh.

Supported in part with funds from the Agency for International Development under contract A.I.D./csd-2822.

Received for publication December 1, 1975.

Revised March 15, 1976.

Accepted March 19, 1976.

Reprint requests: Dr. Balwant Singh, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261.

Table I. Growth-inhibition effect of Lubrifoam on *Neisseria gonorrhoeae* by two methods

*Dilutions**	*Inhibition of growth† after exposure*		
	1 min.	*5 min.*	*10 min.*
Time exposure method			
Undiluted	–	–	–
50%	–	–	–
20%	–	–	–
10%	–	–	–
Control (physiologic saline solution)	+	+	+

	Inhibition of growth† in duplicate plates	
	I	*II*
Plate dilution method		
10%	–	–
5%	–	–
2%	–	–
1%	+	+
Control (physiologic saline solution)	+	+

*Dilutions were prepared in physiologic saline solution. For the plate dilution method, it represents the final concentration in the medium.

†Growth after 24 hours' incubation at 37° C. in a carbon dioxide incubator; + indicates confluent growth, and – indicates complete inhibition of growth.

consideration of requests from several health providers, this study was undertaken to determine the possible effect of certain widely used vaginal lubricants on the in vitro survival of *Neisseria gonorrhoeae.*

Material and methods

Two commercial lubricants commonly available in the United States were used for this study: (1) Lubrifoam,* which is a special aerosol foam lubricant for gynecologic, obstetric, and proctologic use, (Dr. Dunne of the Virginia Health Department, Richmond, Virginia, sent us a container of Lubrifoam for testing); (2) K-Y lubricating jelly,† which is a sterile, water-soluble, widely used lubricating jelly in gynecology and surgery (a sample of K-Y jelly was received from a local sales representative).

Bacterial culture. For preliminary studies, the isolates of *N. Gonorrhoeae* from the local Health Department VD Clinic were used. However, for subsequent final study, working cultures were prepared from frozen stock cultures for each experiment. Bacteria were grown on chocolate agar medium in a carbon dioxide incubator at 37° C. The inoculum was prepared by washing a 24 hour culture from one plate with 1 ml. of trypticase soy broth and adding additional broth to bring it to a standard density of 60 ± 5 per cent transmission as determined by a colorimeter* at 620 mU. The total number of microorganisms was also determined by a spread–plate-count method on chocolate agar medium. *N. gonorrhoeae* cultures were identified by the oxidase test and Gram staining and were confirmed by a sugar fermentation test. Susceptibility to penicillin was also determined with the use of known methods.[4]

Technique for testing bactericidal effect. Three methods were used for determining the bactericidal and bacteriostatic effect of test samples on *N. gonorrhoeae* cultures. Various dilutions of two lubricants were prepared (weight/volume) in physiologic saline solution and thoroughly mixed before testing with a mechanical mixer (Vortex). In preliminary studies, the chocolate agar and the TM selective medium were compared, and the same results were obtained with these two media. Proper controls including physiologic saline solution were used in each experiment. The descriptions of these methods used for testing are given below.

Time-exposure method. To 1 ml. of various dilutions of test samples of the preparation under study, 0.1 ml. of bacterial culture suspension containing 10^6 to 10^7 organisms was added and mixed. After intervals of one, five, and 10 minutes, the mixture was inoculated by streaking on chocolate agar medium plates, with a 3 mm. wire loop. The plates were incubated in a carbon dioxide incubator at 37° C. and examined after 24 hours. The concentration of test material which completely inhibited the visible growth of *N. gonorrhoeae* after any period of exposure was taken as the effective concentration for this exposure interval.

Plate-dilution method. One milliliter of each dilution of the test sample was added to 9 ml. of melted chocolate agar medium at about 50° C., mixed, and poured into 60 by 15 mm. Petri dishes. After the plates were dry, they were inoculated by streaking with a 3 mm. wire loop from a bacterial suspension containing 10^6 to 10^7 colony-forming units (C.F.U.) per 0.1 ml. The plates were incubated in a carbon dioxide incubator at 37° C. and examined after 24 hours. The lowest concentration of test material completely inhibiting the visible bacterial growth was considered the end point.

Plate count method. To an appropriate dilution of the

*Holland-Rantos Co., Inc., 865 Centennial Ave., P. O. Box 5, Piscataway, New Jersey 08854.

†Johnson & Johnson, 500 George St., New Brunswick, New Jersey 08901.

*Spectronic 20, Bausch & Lomb, Inc., 820 Linden Ave., Rochester, New York 14625.

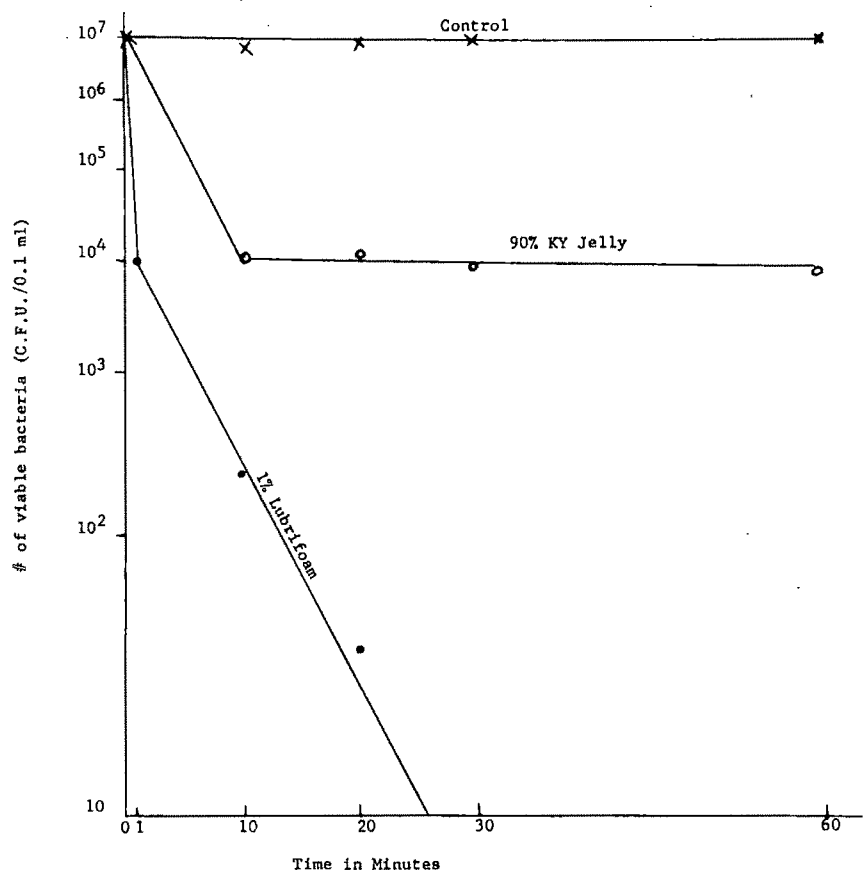


Fig. 1. Bactericidal effect of vaginal lubricants.

test product in physiologic saline solution, a measured amount of bacterial suspension was added and mixed. At specified intervals, a known quantity of mixture was removed for serial dilutions for measurements of surviving number of bacteria, which was determined by the spread–plate-count technique with the use of chocolate agar media plates. The plates were incubated at 37° C. in a carbon dioxide incubator and examined after 24 and 48 hours for counting of the C.F.U.

Results

The bactericidal and bacteriostatic effects of Lubrifoam on *Neisseria gonorrhoeae* are shown in Table I. The undiluted, 50, 20, and 10 per cent concentrations of Lubrifoam in physiologic saline solution were tested by time exposure, and 10, 5, 2, and 1 per cent concentrations in media were tested by the plate-dilution technique. Gonococcal growth was inhibited by all concentrations of Lubrifoam tested by the time-exposure method. Even one-minute contact exposure was sufficient for growth inhibition. The gonococci did not grow after exposure to any of these concentrations of Lubrifoam on chocolate agar medium under optimal growth conditions. For control purposes, the bacteria were treated and exposed in a similar fashion to physiologic saline solution, and a good confluent growth of *N. gonorrhoeae* was obtained after each exposure of one, five, and 10 minutes. In the plate-dilution technique, various dilutions of Lubrifoam were added to the chocolate agar medium, and the final concentrations ranged between 1 and 10 per cent. Inhibition of gonococcal growth was observed only on plates containing 2 and more than 2 per cent final concentrations of Lubrifoam.

The inhibitory effect of Lubrifoam on *Neisseria gonorrhoeae* was also determined by the plate-count method, and the results are shown in Fig. 1. The gonoccocal suspension in trypticase soy broth containing about 10^7 C.F.U. per 0.1 ml. was added to 0.5 ml. of 1 per cent Lubrifoam solution in physiologic saline. After proper mixing, the 0.5 ml. samples were removed immediately, within one minute, and then after 10, 20, 30, and 60 minutes for dilution. The serial tenfold dilutions were prepared each time in physiologic saline solution, and the number of surviving bacteria was determined by the spread–plate-count method with chocolate agar media. The viable bacterial count within one minute decreased from 10^7 to about

Table II. Growth-inhibitory effect of K-Y jelly on different strains of *N. gonorrhoeae*

Test method	Concentration of K-Y jelly* (%)	Growth† of 3 strains after various exposure intervals								
		53258			55528			63220		
		1 min.	5 min.	10 min.	1 min.	5 min.	10 min.	1 min.	5 min.	10 min.
Time-exposed	90	+	+	+	+	+	+	+	+	+
	70	+	+	+	+	+	+	+	+	+
	50	+	+	+	+	+	+	+	+	+
	30	+	+	+	+	+	+	+	+	+
		Growth of 3 strains on duplicate plates								
		I	II		I	II		I	II	
Plate-dilution	10	−	−		−	−		−	−	
	8	+	+		+	+		+	+	
	6	+	+		+	+		+	+	
	4	+	+		+	+		+	+	

*Dilutions made in physiologic saline solution. For the plate-dilution method it represents the final concentration in the medium.

†Growth on chocolate agar medium plate after 24 hours of incubation at 37° C. in a carbon dioxide incubator. + Indicates confluent growth. − Indicates complete inhibition of growth.

10^4 C.F.U. per 0.1 ml. After 10 minutes of contact, the viable gonococcal count was only 10^2 C.F.U. per 0.1 ml. The bactericidal effect was greater with longer periods of contact. For a control, physiologic saline solution was used, and no decrease in viable bacterial count was observed, even after one hour of contact.

The inhibitory effects of K-Y jelly on three different strains of *Neisseria gonorrhoeae* are shown in Table II. By time-exposure method, the K-Y jelly did not have an inhibitory effect on any of these three gonococcal strains. The bacterial culture exposed for 10 minutes, even to undiluted material, grew on chocolate agar medium after proper incubation at 37° C. in carbon dioxide.

By the plate-dilution technique, the K-Y jelly *was inhibitory* to all three strains at a 10 per cent final concentration in the medium; however, concentrations of 9 per cent and below did not interfere with gonococcal growth. Some inhibitory effect of K-Y jelly was also observed by the plate-count method. An aliquot of bacterial suspension was added to 90 per cent K-Y jelly, and, after proper mixing, the number of surviving bacteria were determined at various intervals. Results are shown in Fig. 1. Some decrease in bacterial count was observed when viable bacteria were determined after 10 minutes, but no further significant decrease in bacterial count was noticed when the mixture was plated after 20, 30, or 60 minutes.

Comment

The observations reported here indicate that the growth of *N. gonorrhoeae* isolated from clinical cases is inhibited by exposure to various concentrations of Lubrifoam. The bacteria are killed on contact with Lubrifoam since no growth was observed after inoculation on chocolate agar plates even after one minute of exposure. It is unlikely that the growth inhibition was due to presence of any minute quantity of Lubrifoam still present after the surface of the medium was streaked. In previous studies with vaginal contraceptives and certain noncontraceptive vaginal preparations, it was found that the time-exposure method was a better indicator for bactericidal properties of the test product.[5] By the plate-dilution technique, the gonococci did not grow on chocolate agar media that contained as little as 2 per cent Lubrifoam. The growth inhibition observed by this method when Lubrifoam was added to the chocolate agar medium might have been due to the actual bacteriostatic property of the test product, or the agar medium might have been affected by presence of even small quantities of test product. However, the bactericidal effects of Lubrifoam are very definitely seen by the plate-count method. In this method, a 0.5 ml. quantity of bacterial suspension which had been exposed to 1 per cent Lubrifoam was removed at different intervals, and dilutions were made to determine the count of viable bacteria. During serial dilutions in physiologic saline solution, bacterial cells are washed and any minute quantity of remaining Lubrifoam that might be present is removed. After a longer contact time with Lubrifoam solution, almost all bacteria in the suspension were killed and were unable to grow on chocolate agar medium with all necessary growth supplements.

The K-Y jelly did not show an inhibitory effect on *N. gonorrhoeae* by the time-exposure method. Three dif-

ferent strains of *N. gonorrhoeae*, with various degrees of penicillin resistance, were tested to eliminate any possible differences that might be contributed due to gonococcal strains. All three gonococcal strains did not grow on chocolate agar media containing 10 per cent K-Y jelly. Again, this growth-inhibitory effect might have been due to actual bacteriostatic properties of K-Y jelly or its possible effect in causing some changes in the medium. Nevertheless, some inhibitory effect of K-Y jelly was also found by determining the viable count of bacteria which survived after exposure to 90 per cent K-Y jelly. These in vitro studies indicate that these two vaginal lubricants have a varying degree of bactericidal and bacteriostatic effect on *N. gonorrhoeae*, depending upon the active ingredients. The germicidal effect of certain vaginal lubricants on human and bovine spermatozoa is also known.[6] The spermicidal effects reported by other investigators, and the bactericidal effects observed in the present study are most probably due to a direct action on the cell membrane. Whether these in vitro observations can be applied to the in vivo situation remains to be seen. *Neisseria gonorrhoeae* are quite sensitive to most of the surfactant and other ingredients present in many preparations for vaginal lubrication and contraception. The gonococci are killed on exposure to such vaginal preparations.[5] The fastidious nature of these bacteria is well known, and their growth is affected by many substances. In view of the in vitro findings reported in this study, it is clear that certain vaginal lubricants have bactericidal effects, and their presence can inhibit the growth of *Neisseria gonorrhoeae*.

We wish to thank Miss Gertrude Swab and Miss Shelly Weimert for their technical assistance.

REFERENCES

1. Thayer, J. D., and Martin, J. E., Jr.: Improved medium selective for cultivation of *N. gonorrhoeae* and *N. meningitidis*, Public Health Rep. **81:** 559, 1966.
2. Norins, L. C.: The case of gonococcal serology, J. Infect. Dis. **130:** 677, 1974.
3. Dunne, J. J.: Personal communication.
4. Martin, J. E., Jr., Lester, A., Kellog, D. S., Jr., and Thayer, J. D.: In vitro susceptibility of *N. gonorrhoeae* to nine antimicrobial agents, Appl. Microb. **18:** 21, 1969.
5. Singh, B., Cutler, J. C., and Utidjian, H. M. D.: Studies on the development of a vaginal preparation providing both prophylaxis against venereal disease and other genital infections and contraception, Br. J. Vener. Dis. **48:** 57, 1972.
6. Tagatz, G. E., Okagaki, T., and Sciarra, J. J.: The effect of vaginal lubricants on sperm motility and viability in vitro, AM. J. OBSTET. GYNECOL. **113:** 88, 1972.

Cellular hypersensitivity in patients with adenomatous. hyperplasia and adenocarcinoma of the endometrium

SIDNEY Y. CHEN, M.D.
CARMEL J. COHEN, M.D.
DAVID KOFFLER, M.D.
New York, New York

Cellular hypersensitivity was studied in patients with adenomatous hyperplasia and adenocarcinoma of the endometrium with the use of dinitrochlorobenzene (DNCB) skin tests and inhibition of leukocyte migration by homologous and autologous tumor antigen. Inhibition of leukocyte migration by homologous endometrial carcinoma antigen was found in two of five patients with adenomatous hyperplasia and eight of 11 patients with endometrial adenocarcinoma. A comparable degree of inhibition was found with autologous antigen. DNCB skin reactions were found to be strongly positive in patients with adenomatous hyperplasia, and a lesser degree of reactivity was observed in patients with endometrial adenocarcinoma. No correlation was found between leukocyte migration tests and DNCB reactions, and no correlation was observed between these tests and the age of the patient, clinical stage of disease, or histologic grade of the tumor.

A WIDE VARIETY of in vitro tests have been utilized to assess specific and nonspecific cellular hypersensitivity in patients with malignant tumors. Inhibition of leukocyte migration by homologous and autologous tumor-associated antigens has been demonstrated for a variety of tumors.[1-8] The presence of cellular hypersensitivity as measured by leukocyte migration appears to be a frequent phenomenon, and the antigens utilized exhibit considerable specificity for autologous and/or homologous tumors. Nonspecific alteration of cellular hypersensitivity has been measured by phytohemagglutinin stimulation of lymphocytes in vitro[8] and by dinitrochlorobenzene (DNCB) skin testing in vivo.[8-10] No clear pattern has emerged from these studies to indicate that depression or enhancement of cellular hypersensitivity is related to the natural history of tumor progression.

The purpose of the present study was to measure specific cellular hypersensitivity to tumor-associated antigens with the use of the leukocyte migration test and nonspecific cellular hypersensitivity by skin testing with DNCB in patients with endometrial adenocarcinoma. An attempt was made to correlate the degree of cellular hypersensitivity with certain clinical and histologic parameters.

From the Departments of Obstetrics and Gynecology and Pathology, The Mount Sinai School of Medicine.

Received for publication December 5, 1975.

Revised February 23, 1976.

Accepted March 18, 1976.

Reprint requests: Dr. David Koffler, Department of Pathology, Mt. Sinai School of Medicine, Fifth Ave. and 100th. St., New York, New York 10029.

Materials and methods

Patients. Five patients with adenomatous hyperplasia, 11 patients with endometrial adenocarcinoma, seven patients with squamous cell carcinoma of the cervix, one patient with hydatidiform mole, and five normal women were studied. All patients and control subjects were tested prior to initiation of therapy except for the adenomatous hyperplasia group who were studied immediately after operation.

Leukocyte migration technique. Purified lymphocytes were obtained with the use of a modified Ficoll/Hypaque* gradient followed by passage through sucrose to remove contaminating platelets.[11] Migration assays were performed as previously described,[3] and the migration index (M.I.) was calculated as follows:

$$\text{M.I.} = \frac{\text{area of migration with antigen}}{\text{area of migration without antigen}} \times 100\ (\%).$$

*Winthrop Labs., Div. of Sterling Drug Inc., 90 Park Ave., New York, New York 10016.

Table I. Leukocyte migration indices in patients with adenomatous hyperplasia and adenocarcinoma of endometrium

	Antigen used for inhibition			
	Autologous antigen	*Adenocarcinoma of endometrium*	*Squamous carcinoma of cervix*	*Adenocarcinoma of ovary*
Adenomatous hyperplasia				
Dic*	47.5† (45.8-50.5‡)	54.9 (53.8-56.5)	96.1 (94.2-98.3)	103.2 (103.0-103.5)
Hay	98.0 (97.4-98.8)	95.5 (90.1-104.8)	89.6 (87.7-91.5)	85.9 (83.2-88.7)
Pel	95.0 (91.0-99.5)	101.9 (97.5-106.4)	107.4 (103.4-110.5)	102.9 (101.9-103.8)
LeG	97.1 (94.3-98.9)	103.5 (103.0-103.8)	104.1 (103.9-104.3)	
Sto	42.4 (37.8-44.9)	45.7 (44.8-47.4)		
Endometrial adenocarcinoma				
Lar	32.2 (28.5-35.7)	25.1 (24.8-25.7)	107.7 (97.1-110.5)	
Rie	71.5 (69.3-75.8)	54.3 (48.3-59.1)	112.9 (111.2-115.5)	
Yah	40.4 (38.0-42.5)	35.1 (30.1-41.3)		
Dia	74.8 (69.1-77.3)	89.9 (80.5-94.3)		
Pul	31.0 (29.7-32.5)	33.9 (32.5-36.5)	98.1 (97.4-99.0)	103.1 (99.3-107.0)
Nes	98.8 (92.8-104.7)	102.3 (97.2-107.5)	115.0 (110.2-120.1)	116.2 (109.8-122.9)
Fou	51.5 (47.3-54.7)	60.3 (59.1-62.3)	95.6 (91.7-98.5)	92.1 (90.5-93.7)
Ros	50.1 (46.6-53.0)	49.5 (46.6-52.3)	94.2 (91.0-97.7)	101.9 (99.6-104.1)
Tho	49.7 (46.1-54.4)	49.1 (47.9-50.8)		116.1 (113.7-118.5)
McK	87.6 (81.1-98.4)	72.4 (67.9-79.0)	95.7 (91.6-98.8)	92.0 (90.4-93.2)
Pha	92.3 (89.1-95.5)	86.4 (81.9-91.0)	83.3 (82.8-84.0)	83.1 (81.9-84.5)

*Patient studied.
†Mean expressed as per cent migration.
‡Range of values for four experiments.

Antigens. Homogenates of tumor were prepared from autologous and homologous tissues.[2] Homogenates obtained from cervical squamous cell carcinoma and ovarian papillary serous cystadenocarcinoma were previously shown to be reactive with leukocytes obtained from patients with homologous tumors.

Skin tests. Contact sensitization to DNCB was tested in each patient, and either the skin reactions were recorded as negative or they were graded 1 to 4+ positive.[12]

Results

Leukocyte migration experiments. The M.I.'s for each patient studied from the adenomatous hyperplasia and endometrial adenocarcinoma groups are summarized in Table I. In addition, no inhibition of leukocyte migration was observed in seven patients with squamous cell carcinoma of the cervix or hydatidiform mole or in five normal women.

Skin tests. The results of skin tests are summarized in Table II and compared to the degree of leukocyte migration. All patients with adenomatous hyperplasia had strong DNCB reactions except for one patient who was not reactive. This patient had advanced alcoholic cirrhosis. The skin reaction of the endometrial adenocarcinoma patients was variable and unrelated to the clinical stage of the tumor.

Comment

Patients with endometrial carcinoma manifest a high incidence of cellular hypersensitivity, as measured by inhibition of leukocyte migration, to tumor-associated antigens derived from autologous and homologous tumors. The comparable degree of reactivity of autologous and homologous antigens indicate that a group-specific antigen similar to that found in squamous cell carcinoma of the cervix[2] and papillary serous cystadenocarcinoma of the ovary[3] is involved. The latter extracts, which are active in leukocyte migration tests performed in patients with homologous tumors, showed no inhibition of leukocyte migration in patients with endometrial carcinoma or adenomatous hyperplasia, suggesting that three independent antigen systems are operative in inducing cellular hypersensitivity in patients with these gynecologic tumors.

The considerable body of clinical and histopathologic evidence that adenomatous hyperplasia is a closely related precursor lesion of endometrial carcinoma[13] received further support from these studies. Leukocytes from two of five patients with adenomatous hyperplasia manifested sensitization to antigens derived from endometrial carcinoma as well as to antigens derived from autologous adenomatous hyperplasia tissue. Although insufficient "hyperplasia" antigen was available for testing leukocytes from pa-

Table II. Summary of clinical features, leukocyte migration, and DNCB skin tests in patients with adenomatous hyperplasia and adenocarcinoma of endometrium

Patient	*Age*	*FIGO Stage**	*Histological grade†*	*DNCB reaction‡*	*Leukocyte migration§*
Dic	54	0	–	4+	3+
Hay	48	0	–	3+	0
Pel	39	0	–	3+	0
LeG	41	0	–	0	0
Sto	58	0	–	3+	3+
Lar	55	IA	I	2+	3+
Rie	72	IA	I	3+	3+
Yah	63	IA	I	4+	3+
Dia	62	IA	III	0	0
Pul	66	IB	II	0	3+
Nes	77	IB	I	2+	0
Fou	64	IB	I	2+	2+
Ros	81	IB	III	3+	3+
Tho	46	II	I	0	3+
McK	61	II	II	1+	1+
Pha	62	III	I	3+	0

*International Federation of Gynecology and Obstetrics classification.[16]

†I, Well-differentiated adenocarcinoma; II, moderately differentiated adenocarcinoma; III, poorly differentiated adenocarcinoma.

‡DNCB reactions graded negative (0) to strongly positive (4+).

§Migration index of >80 (0), 70 to 80 (1+), 60 to 70 (2+), and <60 (3+) for inhibition with homologous endometrial carcinoma antigen.

tients with endometrial carcinoma, it is likely that cross-reacting or identical antigen is responsible for the inhibition of leukocyte migration in the two groups of patients.

The DNCB skin test for in vivo delayed hypersensitivity was strongly positive in four of five patients with adenomatous hyperplasia, whereas patients with endometrial carcinoma showed a lesser degree of reactivity. This does not appear to be related to the younger mean age of patients with adenomatous hyperplasia inasmuch as strong reactions were observed in elderly patients and negative or weaker reactions were found in several younger patients. Adequate follow-up data were not available to assess the relationship prognosis to either DNCB reactivity or leukocyte migration. Previous studies indicate that in patients with certain tumors there is a correlation between increased survival and positive DNCB reactions.[10] No relationship between either DNCB reaction or leukocyte migration and clinical stage or histologic grade was found in the present study.

Inhibition of leukocyte migration has been shown to assay "delayed hypersensitivity" as evidenced by skin reaction where the same antigen is used for both the in vivo and in vitro tests. A good correlation was found between the test when streptokinase/streptodornase and purified protein derivative were tested in previously sensitized patients.[5] When patients were immunized with keyhole limpet hemocyanin vigorous skin responses were found in patients with significant inhibition of leukocyte migration.[14] In the present study, the lack of correlation between DNCB skin tests and inhibition of leukocyte migration may indicate that DNCB reactions do not necessarily reflect the degree of sensitization to the tumor-associated antigen of endometrial carcinoma.

At present, inhibition of leukocyte migration appears to be the most specific and reproducible method for detecting cellular hypersensitivity to tumor-associated antigens. Extracts of tumors derived from the colon,[6] cutaneous melanomas,[4] the breast,[5] the lung,[1] the ovary,[3, 7] and the uterine cervix[2] have been shown to possess selective reactivity in the leukocyte migration test. The nature of the antigen responsible for the inhibition of leukocyte migration in patients with gynecologic tumors is presently being studied. The failure of cross-reactivity among antigens derived from tumors of the genital tract in the leukocyte migration test suggest that oncofetal antigens are not of primary importance in this reaction. The absence of inhibition of the extracts when tested with leukocytes from normal women indicates that histocompatibility antigens are probably not involved in this reaction. Preliminary studies indicate that tumor-associated antigens may be detected in fractions of tumor homogenates and may be amenable to concentration in a more purified state.[15] Studies from several other tumors, breast[5] and lung carcinoma,[1] indicate that potassium chloride extracts contain antigens reactive in the leukocyte migration test. The leukocyte migration system may provide a basis for isolating tumor-associated antigens which actively sensitize patients, possibly at a stage prior to the development of infiltration.

REFERENCES

1. Boddie, A. W., Carmack, E., Holmes, E., Roth, J. A., and Morton, D. L.: Inhibition of human leukocyte migration in agarose by KCl extracts of carcinoma of the lung, Int. J. Cancer **15**: 823, 1975.
2. Chen, S., Koffler, D., and Cohen, C. J.: Cellular hypersensitivity in patients with squamous cell carcinoma of the cervix, AM. J. OBSTET. GYNECOL. **121**: 91, 1975.
3. Chen, S., Koffler, D., and Cohen, C. J.: Cell-mediated

immunity in patients with ovarian carcinoma, AM J. OBSTET. GYNECOL. **115:** 467, 1973.
4. Mackie, R. M., Spilg, W. G. S., Thomas, C. E., and Cochran, A. J.: Cell-mediated immunity in patients with malignant melanoma, Br. J. Dermatol. **87:** 523, 1972.
5. McCoy, J. L., Jerome, L. F., Dean, J. H., Cannon, G. B., Alford, T. C., Doering, T., and Herberman, R. B.: Inhibition of leukocyte migration by tumor-associated antigens in soluble extracts of human breast carcinoma, J. Natl. Cancer Inst. **53:** 11, 1974.
6. McIllmurray, M. B., Price, M. R., and Langman, J. S.: Inhibition of leukocyte migration in patients with large intestinal cancer by extracts prepared from large intestinal tumors and from normal colonic mucosa, Br. J. Cancer **29:** 305, 1974.
7. Melnick, H., and Barber, H. R. K.: Cellular immunologic responsiveness to extracts of ovarian epithelial tumors, Gynecol. Oncol. **3:** 77, 1975.
8. Twomey, P. L., Catalona, W. J., and Chretien, P. B.: Cellular immunity in cured cancer patients, Cancer **33:** 435, 1974.
9. Catalona, W. J., and Chretien, P. B.: Abnormalities of quantitative dinitrochlorobenzene sensitization in cancer patients—correlation with tumor stage and histology, Cancer **31:** 353, 1973.
10. Morton, D. L., and Eilber, F. R.: Prognostic significance of cutaneous anergy for the surgical treatment of solid neoplasms, Natl. Cancer Inst. Monogr. **34:** 103, 1971.
11. Bull, D. M., Leibach, J. R., Williams, M. A., and Helms, R. A.: Immunity to colon cancer assessed by antigen-induced inhibition of mixed mononuclear cell migration, Science **181:** 957, 1972.
12. Catalona, W. J., Taylor, P. T., Rabson, A. S., and Chretien, P. B.: A method for dinitrochlorobenzene contact sensitization—A clinicopathological study, N. Engl. J. Med. **286:** 399, 1972.
13. Gusberg, S. B., and Kaplan, A. L.: Precursors of corpus cancer. IV. Adenomatous hyperplasia as stage 0 carcinoma of endometrium, AM. J. OBSTET. GYNECOL. **87:** 662, 1963.
14. Curtis, J. E., and Hersh, E. M.: Cellular immunity in man: Correlation of leukocyte migration inhibition factor formation and delayed hypersensitivity, Cell. Immunol. **8:** 55, 1973.
15. Faiferman, I., Gleicher, N., Cohen, C. J., and Koffler, D.: Unpublished results.
16. The International Federation of Gynecology and Obstetrics: Definitions of the different clinical stages of carcinoma of the corpus uteri, Int. J. Gynecol. Obstet. **9:** 172, 1971.

Fallopian tube and ovarian hydrocarbons

ERIC J. SINGH, PH.D.
FREDERICK P. ZUSPAN, M.D.
IRACEMA M. BACCARINI, M.D.
ATEF MOAWAD, M.D.
Chicago, Illinois

Hydrocarbons of the human ovary and Fallopian tube have been studied by temperature-programmed gas chromatography. The major compounds present are a series of n-alkanes (C_{16} to C_{40}), with the addition of iso and anteiso hydrocarbons. The human ovary and Fallopian tube hydrocarbons did not show significant changes during the menstrual cycle.

HYDROCARBONS of the human ovary and Fallopian tube during the menstrual cycle have not yet been reported. The hydrocarbons of the normal human ovary and Fallopian tube during the menstrual cycle have been studied in this report as well as the effect of ovarian hormones on these substances.

Material and method

Thirty-four normal, healthy female patients of reproductive age were studied. Neither the surgical excised ovary nor Fallopian tube showed pathologic disease. Specimens were obtained from women in different phases of the menstrual cycle (early and late proliferative phases and early and luteal phases). Specimen weights of the tissue studied from the ovary and Fallopian tube ranged from 0.5 to 1.2 Gm. The fresh tissues were rinsed with isotonic saline to remove blood and then homogenized in a Waring Blendor for 2 minutes with 20 ml. of chloroform-methanol (2:1, v/v) per gram net weight of tissue. The lipid was extracted with chloroform-methanol[2] (2:1, v/v). All solvents were of AR grades and redistilled before use.[4]

The hydrocarbons were isolated as described earlier.[2] The saturated and unsaturated hydrocarbons were separated on argentation thin-layer chromatography and further confirmed by spot test.[6] The purity of the components was checked by thin-layer chromatography.[2]

Samples were subjected to temperature programming in a Barber Colman gas chromatograph Model 5000 with dual hydrogen flame detectors. The rate of heating was 2° C. per minute. The two U-shaped glass columns 72 by 0.6 in. O.D. were packed in 3 per cent SE-30 on 80-90 mesh gas chrom P. The injector and detector temperatures were 340° to 350° C., respectively, and the column was varied over 200° to 340° C., and the carrier gas was helium at 65 ml. per minute. The samples were dissolved in ether and volumes of 2 ml. were injected. A normal, iso, and anteiso hydrocarbon standard from C_{16} to C_{36} was used. The tentative assignments for each peak was obtained from retention time. The area of peaks was measured by planimeter.

Results

The total amounts of hydrocarbons during the menstrual cycle were 12 to 12.7 per cent in the human ovary and 11.2 to 11.7 per cent in the Fallopian tube. The compositions of hydrocarbons are presented in Tables I to IV. A comparative study is made between the ovarian and Fallopian tube hydrocarbons during the menstrual cycle. The major portion is normal, saturated hydrocarbons in the range of C_{16} to C_{40} as well as branched-chain members. It is noted from the tables that both saturated even and odd hydrocarbons are present. The major hydrocarbons in the human

From the Department of Obstetrics and Gynecology, University of Chicago.

Supported in part by the Ford Foundation Grant No. 690-0108 A.

Received for publication September 9, 1975.

Accepted March 25, 1976.

Reprint requests: Dr. Frederick P. Zuspan, The Ohio State University, 410 West 10th Ave., Columbus, Ohio 43210.

Table I. Saturated long-chain hydrocarbons of human ovary

	Early proliferative phase (6 cases)			*Late proliferative phase (5 cases)*		
Carbon No.	*Normal**	*Iso**	*Anteiso**	*Normal*	*Iso*	*Anteiso*
16	0.2 ± 0.1†	—	—	0.1 ± 0.0	—	—
17	Tr‡	0.4 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.4 ± 0.1	0.1 ± 0.0
18	0.5 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.6 ± 0.1	0.1 ± 0.0	Tr
19	0.5 ± 0.0	Tr	Tr	0.5 ± 0.1	Tr	Tr
20	1.0 ± 0.2	Tr	Tr	0.9 ± 0.1	0.1 ± 0.0	0.1 ± 0.0
21	2.0 ± 0.2	Tr	0.1 ± 0.0	1.9 ± 0.1	Tr	Tr
22	5.4 ± 0.3	Tr	0.3 ± 0.1	5.6 ± 0.3	Tr	0.2 ± 0.1
23	7.4 ± 0.3	0.3 ± 0.1	0.3 ± 0.0	7.4 ± 0.4	0.3 ± 0.1	0.4 ± 0.1
24	8.7 ± 0.5	0.3 ± 0.1	0.4 ± 0.1	8.2 ± 0.4	0.3 ± 0.1	0.3 ± 0.1
25	9.4 ± 0.5	0.1 ± 0.0	0.3 ± 0.0	9.9 ± 0.6	0.2 ± 0.0	0.2 ± 0.0
26	7.4 ± 0.4	0.4 ± 0.1	0.8 ± 0.2	7.4 ± 0.5	0.2 ± 0.1	1.0 ± 0.2
27	7.6 ± 0.6	0.3 ± 0.1	0.8 ± 0.2	7.0 ± 0.5	0.4 ± 0.1	0.8 ± 0.2
28	8.0 ± 0.7	0.3 ± 0.1	0.6 ± 0.1	8.4 ± 0.6	0.4 ± 0.1	0.6 ± 0.2
29	7.0 ± 0.2	0.3 ± 0.1	0.6 ± 0.2	7.0 ± 0.4	0.3 ± 0.1	0.6 ± 0.2
30	6.7 ± 0.2	0.1 ± 0.0	0.5 ± 0.3	6.7 ± 0.2	0.2 ± 0.1	0.4 ± 0.1
31	6.1 ± 0.3	0.1 ± 0.0	0.6 ± 0.2	6.2 ± 0.4	Tr	0.4 ± 0.1
32	4.0 ± 0.2	0.1 ± 0.0	0.3 ± 0.1	3.8 ± 0.2	0.1 ± 0.0	0.5 ± 0.1
33	3.4 ± 0.2	0.1 ± 0.0	0.3 ± 0.0	3.0 ± 0.2	0.2 ± 0.1	0.4 ± 0.1
34	1.9 ± 0.2	Tr	0.1 ± 0.0	1.8 ± 0.1	0.1 ± 0.0	0.1 ± 0.0
35	1.0 ± 0.2	0.1 ± 0.0	0.1 ± 0.0	0.8 ± 0.2	0.2 ± 0.1	0.2 ± 0.0
36	0.6 ± 0.1	0.3 ± 0.1	Tr	0.6 ± 0.1	0.1 ± 0.0	Tr
37	0.6 ± 0.1	0.1 ± 0.0	—	0.8 ± 0.1	0.1 ± 0.0	—
38	0.4 ± 0.1	Tr	—	0.5 ± 0.0	0.1 ± 0.0	—
39	0.1 ± 0.0	—	—	0.1 ± 0.0	—	—
40	0.5 ± 0.0	—	—	0.4 ± 0.0	—	—

*Amount in per cent of total hydrocarbons. †± S.D. ‡Tr = trace.

Table II. Saturated long-chain hydrocarbons of human ovary

	Early secretory phase (4 cases)			*Late secretory phase (3 cases)*		
Carbon No.	*Normal**	*Iso**	*Anteiso**	*Normal*	*Iso*	*Anteiso*
16	0.1 ± 0.0†	—	—	Tr	—	—
17	Tr‡	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.5 ± 0.1	Tr
18	0.5 ± 0.1	Tr	Tr	0.4 ± 0.1	Tr	Tr
19	0.4 ± 0.1	Tr	Tr	0.6 ± 0.1	Tr	Tr
20	0.8 ± 0.1	Tr	Tr	0.7 ± 0.1	Tr	Tr
21	1.9 ± 0.1	Tr	Tr	1.8 ± 0.2	Tr	Tr
22	6.0 ± 0.3	0.1 ± 0.0	0.2 ± 0.1	6.8 ± 0.4	0.1 ± 0.0	0.2 ± 0.0
23	7.8 ± 0.6	0.2 ± 0.0	0.2 ± 0.0	7.9 ± 0.7	0.2 ± 0.0	0.2 ± 0.0
24	9.0 ± 0.5	0.4 ± 0.1	0.4 ± 0.7	9.0 ± 0.7	0.4 ± 0.1	0.4 ± 0.1
25	9.5 ± 0.8	Tr	0.3 ± 0.1	10.5 ± 0.9	Tr	0.4 ± 0.1
26	7.7 ± 0.6	0.2 ± 0.0	0.7 ± 0.1	8.0 ± 0.7	0.4 ± 0.2	0.8 ± 0.1
27	7.2 ± 0.4	0.2 ± 0.0	0.7 ± 0.2	7.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.1
28	7.5 ± 0.3	0.3 ± 0.1	0.7 ± 0.3	7.7 ± 0.4	0.2 ± 0.1	0.6 ± 0.2
29	7.0 ± 0.4	0.3 ± 0.1	0.4 ± 0.1	6.8 ± 0.3	0.2 ± 0.1	0.5 ± 0.1
30	6.5 ± 0.3	0.2 ± 0.0	0.4 ± 0.1	7.0 ± 0.5	0.2 ± 0.1	0.3 ± 0.0
31	6.5 ± 0.4	0.1 ± 0.0	0.4 ± 0.1	6.0 ± 0.2	Tr	0.5 ± 0.2
32	5.0 ± 0.2	0.1 ± 0.0	0.2 ± 0.0	5.7 ± 0.3	Tr	0.4 ± 0.0
33	3.6 ± 0.3	Tr	0.2 ± 0.0	3.0 ± 0.2	Tr	0.2 ± 0.0
34	1.5 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	1.6 ± 0.2	0.1 ± 0.0	0.1 ± 0.0
35	0.6 ± 0.0	0.1 ± 0.0	0.2 ± 0.1	0.7 ± 0.1	Tr	0.1 ± 0.0
36	0.4 ± 0.1	Tr	—	0.2 ± 0.0	Tr	—
37	0.5 ± 0.1	0.1 ± 0.0	—	0.4 ± 0.1	0.1 ± 0.0	—
38	0.4 ± 0.0	0.1 ± 0.0	Tr	0.3 ± 0.1	0.1 ± 0.0	Tr
39	Tr	—	—	Tr	—	—
40	0.3 ± 0.0	—	—	0.2 ± 0.0	—	—

*Amount in per cent of total hydrocarbons. †± S.D. ‡Tr = trace.

Table III. Human Fallopian tube saturated hydrocarbons during menstrual cycle

	Early proliferative phase (5 cases)			*Late proliferative phase (5 cases)*		
Carbon No.	*Normal**	*Iso**	*Anteiso**	*Normal*	*Iso*	*Anteiso*
16	1.2 ± 0.2†	—	—	1.0 ± 0.2	—	—
17	0.7 ± 0.1	0.8 ± 0.1	0.3 ± 0.0	0.9 ± 0.1	0.8 ± 0.1	0.2 ± 0.1
18	1.1 ± 0.1	Tr‡	0.1 ± 0.0	1.2 ± 0.2	Tr	Tr
19	0.9 ± 0.1	0.1 ± 0.0	—	1.0 ± 0.1	0.1 ± 0.0	Tr
20	1.1 ± 0.1	Tr	0.2 ± 0.0	1.1 ± 0.1	Tr	0.3 ± 0.1
21	1.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	1.1 ± 0.1	Tr	0.1 ± 0.0
22	2.1 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	2.2 ± 0.3	0.2 ± 0.1	0.2 ± 0.0
23	2.9 ± 0.2	0.3 ± 0.1	0.5 ± 0.1	2.8 ± 0.3	0.3 ± 0.1	0.5 ± 0.1
24	3.6 ± 0.1	0.3 ± 0.0	0.3 ± 0.1	3.9 ± 0.3	0.2 ± 0.0	0.4 ± 0.1
25	5.4 ± 0.2	0.5 ± 0.1	0.7 ± 0.1	5.5 ± 0.2	0.4 ± 0.1	0.7 ± 0.1
26	5.9 ± 0.4	0.5 ± 0.0	0.7 ± 0.1	5.2 ± 0.1	0.6 ± 0.1	0.9 ± 0.2
27	7.1 ± 0.5	0.7 ± 0.1	0.8 ± 0.2	7.5 ± 0.5	0.7 ± 0.2	0.8 ± 0.2
28	7.6 ± 0.6	1.1 ± 0.2	0.9 ± 0.2	7.0 ± 0.6	1.2 ± 0.3	0.9 ± 0.2
29	6.1 ± 0.3	0.8 ± 0.1	0.3 ± 0.0	6.6 ± 0.4	0.5 ± 0.1	0.6 ± 0.1
30	7.1 ± 0.6	0.3 ± 0.0	0.5 ± 0.1	7.0 ± 0.4	0.4 ± 0.0	0.5 ± 0.1
31	6.9 ± 0.4	0.5 ± 0.1	1.0 ± 0.2	7.0 ± 0.4	0.5 ± 0.2	1.1 ± 0.2
32	6.3 ± 0.2	0.3 ± 0.0	0.7 ± 0.2	6.0 ± 0.2	0.3 ± 0.1	0.7 ± 0.1
33	5.9 ± 0.2	0.3 ± 0.1	0.9 ± 0.2	6.2 ± 0.3	0.6 ± 0.1	0.6 ± 0.2
34	2.9 ± 0.2	0.3 ± 0.1	0.3 ± 0.0	3.0 ± 0.1	0.2 ± 0.1	0.3 ± 0.0
35	2.5 ± 0.1	0.3 ± 0.0	0.3 ± 0.0	2.5 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
36	1.3 ± 0.1	0.5 ± 0.1	0.3 ± 0.1	1.2 ± 0.0	0.4 ± 0.1	0.4 ± 0.1
37	1.1 ± 0.0	0.1 ± 0.0	Tr	1.0 ± 0.1	0.1 ± 0.0	Tr
38	0.5 ± 0.1	0.2 ± 0.0	Tr	0.5 ± 0.0	0.1 ± 0.0	Tr
39	0.5 ± 0.0	0.1 ± 0.0	—	0.5 ± 0.1	0.2 ± 0.0	—
40	0.4 ± 0.0	—	—	0.4 ± 0.1	—	—

*Amount in per cent of total hydrocarbons. †± S.D. ‡Tr = trace.

Table IV. Human Fallopian tube saturated hydrocarbons during menstrual cycle

	Early luteal phase (3 cases)			*Late luteal phase (3 cases)*		
Carbon No.	*Normal**	*Iso**	*Anteiso**	*Normal*	*Iso*	*Anteiso*
16	1.0 ± 0.1†	—	—	1.0 ± 0.0	—	—
17	0.5 ± 0.0	0.6 ± 0.1	0.1 ± 0.0	0.5 ± 0.1	0.7 ± 0.1	0.2 ± 0.0
18	1.0 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	1.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0
19	1.0 ± 0.2	Tr‡	Tr	1.2 ± 0.0	Tr	Tr
20	1.2 ± 0.1	Tr	0.2 ± 0.0	1.2 ± 0.1	Tr	0.3 ± 0.1
21	1.0 ± 0.1	Tr	Tr	1.2 ± 0.1	Tr	Tr
22	2.0 ± 0.2	0.2 ± 0.0	0.2 ± 0.0	1.9 ± 0.2	0.1 ± 0.0	0.1 ± 0.0
23	3.0 ± 0.2	0.2 ± 0.0	0.4 ± 0.1	3.2 ± 0.3	0.2 ± 0.0	0.5 ± 0.1
24	4.0 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	4.2 ± 0.3	0.3 ± 0.1	0.3 ± 0.1
25	5.0 ± 0.3	0.4 ± 0.1	0.6 ± 0.1	5.0 ± 0.4	0.5 ± 0.1	0.6 ± 0.0
26	6.0 ± 0.4	0.5 ± 0.1	0.8 ± 0.2	5.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.1
27	7.0 ± 0.3	0.7 ± 0.2	0.9 ± 0.1	7.5 ± 0.6	1.0 ± 0.1	0.9 ± 0.2
28	8.1 ± 0.5	1.0 ± 0.1	0.9 ± 0.2	7.6 ± 0.6	0.8 ± 0.1	0.8 ± 0.2
29	7.0 ± 0.6	0.7 ± 0.1	0.4 ± 0.0	6.5 ± 0.4	0.5 ± 0.1	0.4 ± 0.0
30	6.5 ± 0.3	0.4 ± 0.2	0.5 ± 0.1	6.8 ± 0.2	0.5 ± 0.2	0.5 ± 0.1
31	6.0 ± 0.4	0.4 ± 0.1	0.7 ± 0.0	6.7 ± 0.4	0.6 ± 0.2	0.8 ± 0.1
32	6.0 ± 0.2	0.4 ± 0.0	0.8 ± 0.1	5.8 ± 0.4	0.5 ± 0.1	0.9 ± 0.0
33	6.0 ± 0.1	0.4 ± 0.1	0.8 ± 0.1	5.5 ± 0.2	0.5 ± 0.0	0.7 ± 0.1
34	4.0 ± 0.2	0.3 ± 0.3	0.3 ± 0.1	3.5 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
35	3.0 ± 0.1	0.4 ± 0.0	0.2 ± 0.0	2.4 ± 0.1	0.4 ± 0.0	0.3 ± 0.0
36	2.0 ± 0.0	0.4 ± 0.0	0.3 ± 0.1	1.7 ± 0.0	0.3 ± 0.0	0.3 ± 0.1
37	1.0 ± 0.1	0.2 ± 0.0	0.1 ± 0.0	0.5 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
38	0.5 ± 0.1	—	Tr	0.6 ± 0.0	—	Tr
39	0.5 ± 0.0	—	—	0.3 ± 0.1	0.5 ± 0.1	—
40	0.5 ± 0.1	—	—	0.3 ± 0.1	—	—

*Amount in per cent of total hydrocarbons. †± S.D. ‡Tr = trace.

ovary during the menstrual cycle are n-tricosane (C_{23}), n-tetracosane (C_{24}), n-pentacosane (C_{25}), n-hexacosane (C_{26}), n-heptacosane (C_{27}), n-octacosane (C_{28}), and n-nonacosane (C_{29}). The fallopian tube has n-heptacosane (C_{27}), n-octacosane, n-nonacosane, n-triacosane (C_{30}), and n-heneitriacontane (C_{31}). Tables I to IV show that the percentage compositions of ovarian hydrocarbons are different from those of Fallopian tube hydrocarbons during the menstrual cycle. The ovary is saturated with more anteiso hydrocarbons than iso hydrocarbons, whereas this condition is not as prominent in the fallopian tube.

Comment

Hydrocarbons are integral components of both the human ovary and Fallopian tube with three different kind of series. The total amounts of even and odd normal hydrocarbons are in the ratio of 1 : 1 in both tissues. Both tissues have a greater amount of anteiso hydrocarbons than iso hydrocarbons.

Compositional cyclic variations of hydrocarbons occur during the menstrual cycle, but these variations are not significant. The exact role of hydrocarbons in these reproductive tissues still remains to be established.

REFERENCES

1. Singh, E. J., and Zuspan, F. P.: Studies on hydrocarbons of human amniotic fluid, J. Am. Oil Chem. Soc. **51:** 280A, 1974.
2. Singh, E. J., and Zuspan, F. P.: Amniotic fluid lipids in normal human pregnancy, AM. J. OBSTET. GYNECOL. **117:** 919, 1973.
3. Singh, E. J., and Zuspan, F. P.: Content of amniotic fluid prostaglandins in normal, diabetic, and drug-abuse pregnancy, AM. J. OBSTET. GYNECOL. **119:** 623, 1974.
4. Singh, E. J., and Zuspan, F. P.: Silica gel impregnated glass fiber paper chromatography for the separation and identification of prostaglandins, J. Chromatogr. Sci. **13:** 188, 1975.
5. Singh, E. J., Baccarini, I. M., and Zuspan, F. P.: Levels of prostaglandins F_2 and E_2 in human endometrium during its menstrual cycle, AM. J. OBSTET. GYNECOL. **121:** 1003, 1975.
6. Singh, E. J., and Zuspan, F. P.: Spot test for detection of saturated and unsaturated fatty acids, J. Chem. Educ. **50:** 669, 1973.

Human Ovulation: Mechanisms, prediction, detection, and regulation

An international symposium has been organized on "Human Ovulation." The symposium will be held at the C. S. Mott Center for Human Growth and Development, Wayne State University School of Medicine, Detroit, Michigan, on April 19-21, 1977 (following the World Congress on Fertility and Sterility, Miami Beach, Florida). Forty-three national and international experts will discuss oogenesis; folliculogenesis; structure, ultrastructure, and scanning electron microscopy of ovulation; endocrine, neuroendocrine, and neuromuscular mechanisms of ovulation; intrafollicular endocrine profiles; types of anovulation; physical, biophysical, and endocrine techniques to predict and detect ovulation; ovarian ultrasonics; induction of ovulation by clomiphene, gonadotropins, or GnRH; regularization of ovulation; treatment of cycles with corpus luteum defects or polycystic ovaries; and cervical mucus, symptothermal methods, and lactational amenorrhea in relation to natural family planning. The symposium is accredited by the American Medical Association. Deadline to submit abstracts of contributed research papers is November 1, 1976. For abstract forms and additional information, write: Dr. E. S. E. Hafez, Reproduction Physiology Laboratories, C. S. Mott Center for Human Growth and Development, Wayne State University School of Medicine, Detroit, Michigan 48201. Telephone: (313) 577-1011.

Progestational activity of Danazol in the human female subject

ANNE COLSTON WENTZ, M.D.
GEORGEANNA SEEGAR JONES, M.D.
KARAN C. SAPP
THEODORE M. KING, M.D., PH.D.
Baltimore, Maryland

A progestational action of Danazol has not been reported in the human subject. Danazol administration for 1 month suppressed serum FSH and estradiol values, and the midcycle LH surge; ovulation promptly resumed after treatment. Administration to patients with polycystic ovarian disease resulted in increased LH values, elevated basal temperature, secretory findings in the endometrial biopsy, and menses. Ovarian biopsy did not document corpus luteum formation, and plasma progesterone did not rise. Administration of Danazol to an ovariectomized patient pretreated with estrogen resulted in an atypical endometrial secretory change. Clinical responses to Danazol may in part be explained by a progestational-like effect of the drug.

DANAZOL, THE 2,3-isoxasol derivative of 17α-ethinyltestosterone, has been shown in animals to be antigonadotropic with weak androgenic properties, and to have no estrogenic, antiestrogenic, progestational, antiprogestational, or antiandrogenic activity.[1, 2] In human subjects, a weak androgenic effect is seen but the antigonadotropic activity has been less well observed; decreased levels of follicle-stimulating hormone (FSH) and absence of the midcycle luteinizing hormone (LH) surge occur after chronic Danazol administration.[3–5] The agent has been used in the therapy of cystic mastitis, precocious puberty, and endometriosis, and has been proposed as a potential contraceptive agent. In our ongoing studies to elucidate the mechanism of action of Danazol, we have observed findings suggestive of a progestational activity in human subjects. It is the purpose of this report to outline this clinical evidence.

From the Division of Reproductive Endocrinology, the Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine.
Received for publication December 22, 1975.
Revised March 1, 1976.
Accepted March 18, 1976.
Reprint requests: Anne Colston Wentz, M.D., Dept. of Gynecology and Obstetrics, Woman's Clinic, Rm. 424, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

Materials and methods

Danazol was prepared in 200 mg. capsules and administered orally in divided doses. Informed consent was obtained from all patients and volunteers. Protocols are listed in the order in which undertaken.

One month chronic administration. Four healthy, normal ovulating women received Danazol, 800 mg. per day, for 28 days, and one received 200 mg. per day for 28 days. Blood samples were drawn daily for 5 to 6 days of each week, and analyzed for serum FSH and LH and plasma estradiol and progesterone. Basal temperature charts were kept, and an endometrial biopsy was obtained in one volunteer 15 days after stopping the medication.

"Ovulation induction" studies. Patients thought to have polycystic ovarian disease (PCOD) with elevated baseline LH and normal baseline FSH levels were given Danazol, 200 or 400 mg. per day, for from 3 to 10 days, to ascertain if a decrease in the LH level would normalize hormonal parameters and permit FSH stimulation of follicular development leading to ovulation. Basal temperature charts were kept, and blood samples were drawn daily for measurement of serum FSH and LH, plasma estradiol, and progesterone. Endometrial biopsies were obtained after basal temperature had been elevated for several days and analyzed for secretory effect.

Ovarian biopsy studies. Selected patients with clini-

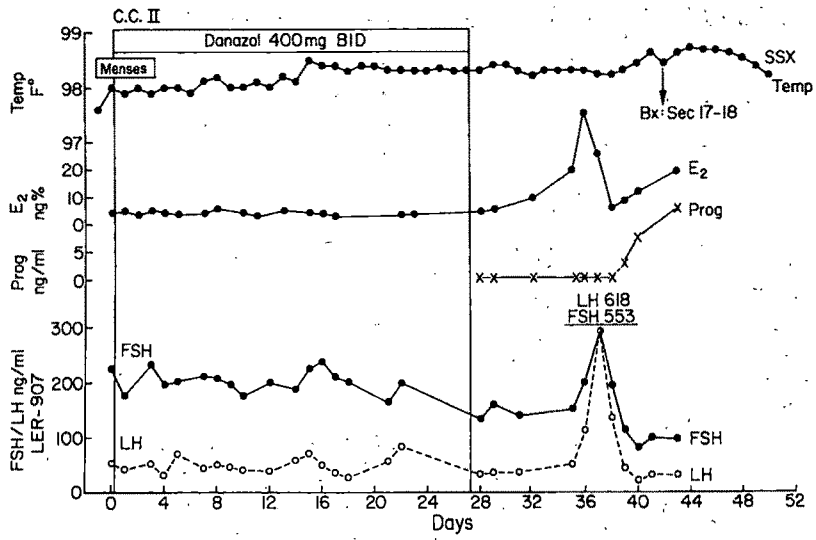


Fig. 1. Daily hormonal parameters observed during chronic administration of Danazol, 800 mg. per day. FSH levels were decreased, but no change was observed in estradiol or LH. Ovulation occurred 9 days after discontinuation of Danazol. *S* = spotting; *X* = bleeding.

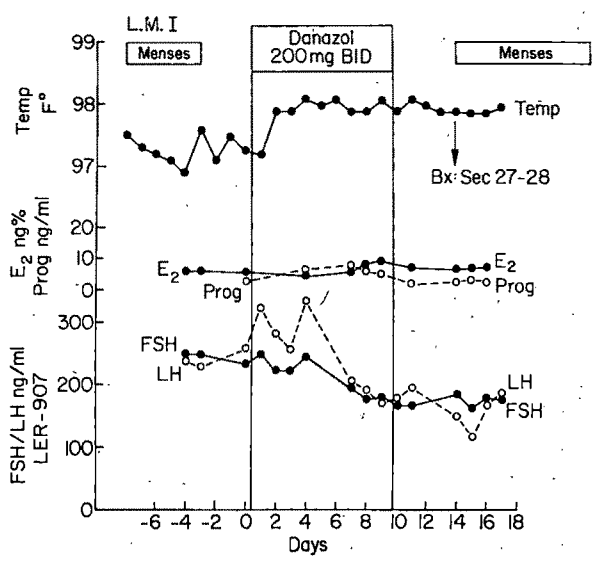


Fig. 2*A*. Response to Danazol in polycystic ovarian disease. An elevated basal temperature, increased serum LH, and secretory endometrial biopsy suggested that ovulation had occurred. Steroid values obtained later showed no increase in estradiol, estrone, or progesterone, suggesting a progestational effect of the drug.

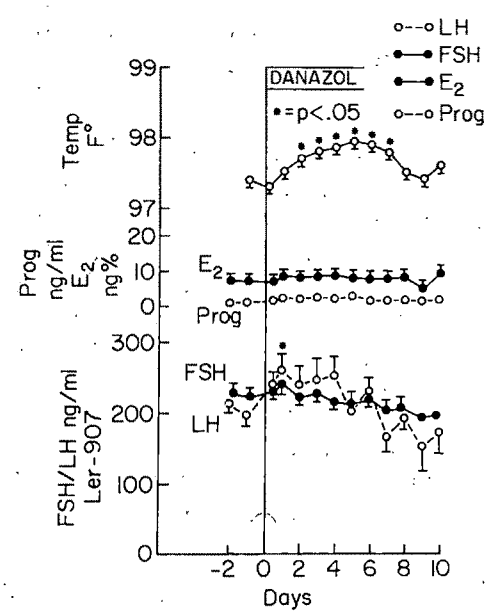


Fig. 2*B*. Hormone patterns and basal temperature changes in 10 treatment cycles in seven patients. Each point represents the mean ± S.E.M. The asterisks represent a difference from baseline, $p < 0.05$.

cally diagnosed polycystic ovarian disease who were to undergo wedge resection of the ovaries were given Danazol as described above, and wedge biopsy of the ovaries was carried out between 7 to 10 days after onset of Danazol administration. At laparotomy, ovaries were observed for evidence of corpora lutea, and biopsy material was reviewed for evidence of follicular development and corpora lutea.

Follicular phase study. Two healthy, ovulating women took Danazol, 800 mg. per day for 7 days from cycle days 4 to 10, and an endometrial biopsy was obtained on days 10 and 11, respectively. Three women took Danazol, 200 mg. per day for 7 days from cycle days 6 or 7, and an endometrial biopsy was obtained on cycle days 12, 13, and 15, respectively. Blood hormone values were drawn as described above.

Table I. Clinical and hormonal findings in patients with polycystic ovarian disease receiving short-term, low-dose Danazol

Patient	*Danazol dosage (mg./day × no. of days)*	*Increased basal temp.*	*Increased serum LH*	*Increased plasma progesterone*	*Increased plasma estradiol*	*Day of biopsy**	*Biopsy result*	*Day of bleeding*	*Comment*
L. M.—I	400 × 10	Yes	Yes	No	No	14	Sec. 27-28	16	Biopsy revised "atypical secretory effect"
II	400 × 2	Yes	Yes	After progesterone admin.	N.A.†	10	Sec. 25-26	19	On progesterone supp.
III	400 × 5	Yes	Yes	No	No	N.A.	N.A.	8	
IV	400 × 2	Yes	Yes	After progesterone admin.	N.A.	13	Sec. 22-23	20	On progesterone supp.
E. W.	400 × 10	Yes	Yes	No	No	11	Atypical secretory effect	13	
M. K.	200 × 10	Yes	Yes	No	No	7	Interval	11	
B. W.—I	200 × 10	Yes	Yes	No	No	7	Sec. 16-17	14	Spotted days 9-13
C. M.	200 × 10	Yes	No	No	No	7	Sec. 16-17	14	
V. F.—I	200 × 10	Yes	Yes	To 7 ng./ml. on days 2, 5, 6	No	9	Proliferative	16	
	200 × 6	N.A.	No	N.A.	N.A.	N.A.	N.A.	8	Noncompliant
D. R.	200 × 10	Yes	No	No	No	12	Glandular-stromal disparity	13	

*Day 1 = first Danazol dose.
†N.A. = Not available.

Table II. Clinical findings in patients with polycystic ovarian disease who underwent ovarian wedge biopsy after receiving Danazol

Patient	*Danazol dosage (mg./day × no. of days)*	*Increased basal temp.*	*Increased serum LH*	*Increased plasma progesterone*	*Increased plasma estradiol*	*Day of bleeding*	*Day of surgery**	*Endometrial biopsy*	*Ovarian findings*
L. M.—V	400 × 4	Yes	N.A.	N.A.	N.A.	Day before surgery	Bleeding		Anovulatory ovaries
B. W.—II	200 × 7	N.A.	N.A.	N.A.	N.A.	11	Sec. 17-18		? early CL with bilateral diffuse theca luteinization
C. W.	200 × 7	Yes	Yes	No	Yes	9	7	Sec. 17-18	Compatible with PCOD
G. C.	200 × 7	N.A.	Yes	Yes	No	N.A.	7	Sec. with bleeding and repair	Normal CL > 24 days
L. H.	400 × 7	N.A.	N.A.	N.A.	No	N.A.	7	Sec. 16-17	Compatible with PCOD polyovular follicle in right ovary
M. S.	400 × 6	N.A.	Yes	No	No	N.A.	6	Proliferative	Compatible with PCOD polyovular follicles in right ovary

*Day 1 = first Danazol dose.

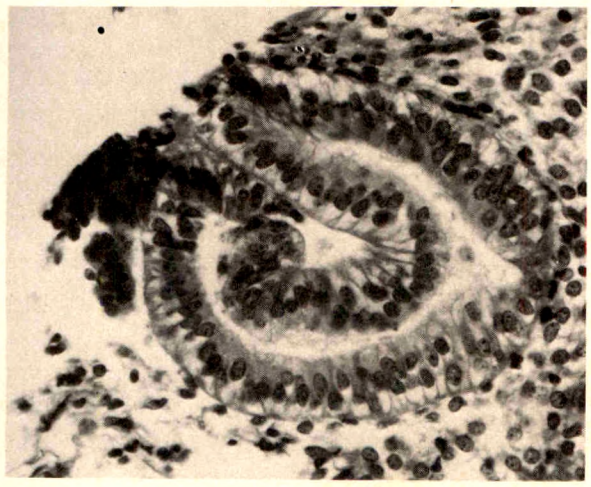


Fig. 3*A*. Endometrial biopsy in Patient C. M. (Hematoxylin and eosin; ×490.) Subnuclear vacuoles, early evidence of a secretory effect, are seen.

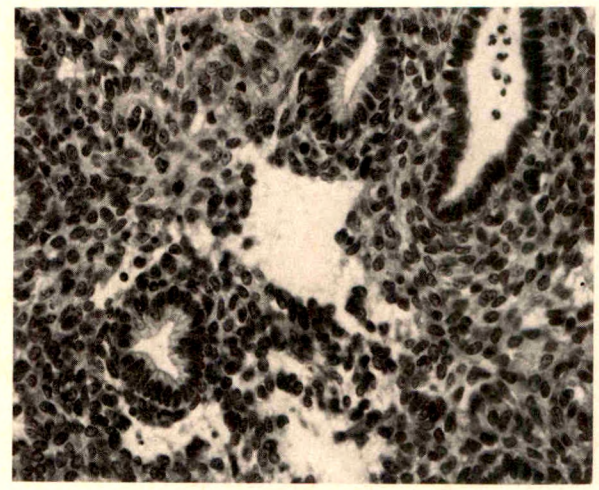


Fig. 3*B*. Decidual response observed in Patient L. M.—I. (Hematoxylin and eosin; ×390.)

One patient, ovariectomized because of bilateral dermoid cysts, and on cyclic stilbestrol 0.1 mg. per day for menopausal symptomatology, consented to take Danazol 200 mg. per day on days 18 to 25 of estrogen therapy. An endometrial biopsy was obtained as previously scheduled on day 25.

Results

A. Four volunteers taking Danazol 800 mg. per day for 28 days showed no change in baseline LH, but an LH surge was not observed. Estradiol values remained low without increase except in one woman, but an LH surge was not triggered. No rise in progesterone was seen. Basal temperatures were monophasic but in the range of 98° F., slightly higher than usually seen in the follicular phase. Results representative of this group are shown in Fig. 1.

Following discontinuation of Danazol, all four women ovulated, as confirmed from endometrial biopsy or LH results, and a normal ovulatory menses in 4 to 5 weeks. One woman spotted for the duration of Danazol administration, and another had 5 days of bleeding 9 days after stopping Danazol, without an increase in plasma progesterone levels or other evidence of ovulation. Endometrial biopsies were not obtained during Danazol administration.

B. One woman taking Danazol 200 mg. per day for 28 days appeared to ovulate normally on cycle day 12, as confirmed by an endometrial biopsy read as secretory day 25 to 26 taken 2 days before menses, and a rise in progesterone values. The estradiol surge occurred normally, although the day of the LH surge was not sampled.

C. Fig. 2*A* illustrates findings that suggested triggering of ovulation within 48 hours of Danazol administration in a patient with clinical polycystic ovarian disease (PCOD). Parameters initially observed included an abrupt rise in basal temperature, increased LH, a secretory endometrial biopsy, and normal menses. Three subsequent treatment cycles resulted in similar findings, although pregnancy did not occur. Retrospective analysis of plasma progesterone showed no increase following "ovulation," and plasma estradiol did not increase either before the LH increase or prior to menses.

Six additional patients, similarly treated, showed comparable hormonal results (Fig. 2*B*), and clinical findings are summarized (Table I). An increase in basal temperature and serum LH was ordinarily observed within 48 to 72 hours of Danazol administration. The endometrial biopsy, if obtained, showed early secretory changes (Figs. 3*A* and 3*B*) in the absence of any increase in plasma progesterone. V. F. was the only patient to have a proliferative endometrial biopsy, which is particularly difficult to explain as her baseline plasma progesterone level was higher than ordinarily observed and increased on 3 separate days to 7 ng. per milliliter before the biopsy was performed. Her endometrium is responsive to progesterone, as ovulation has been documented following clomiphene.

D. Six patients, previously scheduled for ovarian wedge biopsy, took Danazol prior to laparotomy, with findings summarized in Table II. G. C., with a corpus luteum (CL), was the only patient to receive an infusion of luteinizing hormone–releasing hormone (LRH) prior to surgery, and the luteal development was compatible with ovulation triggered by LH stimulated by LRH (Fig. 4). Patients L. M. and B. W. had received

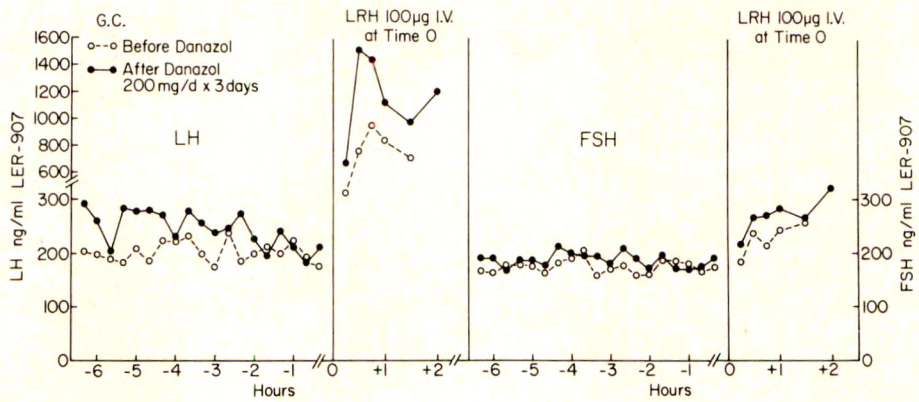


Fig. 4. Gonadotropin parameters following LRH administration before and after Danazol administration.

Table III. Findings in volunteers receiving Danazol during the follicular phase

Volunteer	*Danazol dosage* (*mg./day × no. of days*)	*Cycle days*	*Day of biopsy**	*Day of ovulation* (*LH peak*)	*Biopsy reading*
A. P.—III	800 × 7	4-10	10	23	Bleeding with repair
L. W.—I	800 × 7	4-10	11	17	Atypical secretory effect
Ma.—III	200 × 7	6-12	13	14	Interval
A. P.—II	200 × 7	7-13	15	? 24	Insufficient tissue
S. D.—III	200 × 7	7-13	12	15	Interval

*Day 1 = first day of cycle.

Danazol in previous cycles. The ovaries in L. M. showed no evidence of recent or past ovulation, and were small. B. W. had diffuse theca luteinization, and a poorly differentiated structure not conclusively diagnosed histologically as CL. L. H. had a well-developed follicle that appeared preovulatory, and a secretory 16 to 17 day endometrium.

E. Five volunteers received Danazol for 7 days during the follicular phase. In three volunteers changes compatible with a progestational effect were observed *before* ovulation was documented by hormonal evaluation (Fig. 5, Table III). One volunteer, tested in two cycles, was still spotting on cycle day 10 when the biopsy was obtained, and had insufficient tissue for examination in the next study; her ovulation was significantly delayed in both cycles. Basal temperature increased in four of five women on temperature charts.

The ovariectomized women had endometrial findings of early secretory change, with subnuclear vacuoles and an atypical secretory pattern (Fig. 6).

Comment

A progestational effect of Danazol has not been reported previously in human subjects. Animal testing designed to elaborate the hormonal profile of the drug suggested that Danazol has no progestational activity based on its inability, when administered orally, to induce a progestational change in immature female rabbits pretreated with estrogen and evaluated by the Clauberg method. Dmowski and colleagues[1] reported the finding of an atypical progestational effect in rabbits receiving parenteral Danazol, but concluded that "typical secretory changes in the glandular epithelium were not revealed by microscopic examination." Potts, Beyler, and Shane[2] suggested that "the endometrial response . . . is apparently an androgenic response in the Clauberg assay." For this reason, Danazol has been considered an antigonadotropin and weak androgen, although evidence for a direct effect upon gonadotropin output has not been presented. The results in G. C., tested with LRH before and after Danazol administration, show that Danazol does not inhibit the release of gonadotropin to provocative stimulation at the pituitary level (Fig. 4).

A progestational effect in endometrial biopsy material cannot be diagnosed without caution. All endometrial biopsies were dated by the criteria of Noyes, Hertig, and Rock[6] which state that one may not safely diagnose ovulation on the basis of a few small, scattered vacuoles. As indicated in Tables I and II, most endometrial biopsies were dated as secretory day 16 to 17 or more, indicating that greater than 50 per cent of endometrial glands observed had subnuclear vacuoles. The description "atypical secretory change" refers to

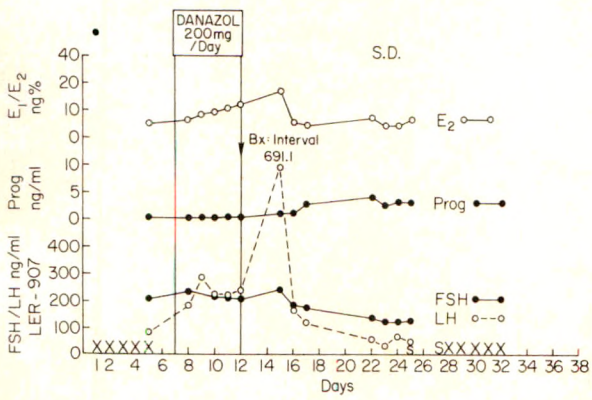


Fig. 5. Follicular phase Danazol administration caused secretory changes in the endometrial biopsy obtained *before* the LH surge.



Fig. 6. Endometrial biopsy in an ovariectomized patient receiving Danazol after estrogen pretreatment. (Hematoxylin and eosin; ×480.)

the finding of areas of glandular-stromal disparity, where decidual response is seen in the presence of less well-developed endometrial glands. Thus, biopsies observed presented evidence of early secretory change, or a decidual response, either of which is characteristic of progesterone or progestin influence.

The effects observed after Danazol administration may be explained by a progestational activity. Such agents may prevent an LH surge without producing much change in baseline LH levels, although decreased FSH values have been documented. Most progestational agents, except dydrogesterone and ethisterone, cause an elevated basal temperature. Goldenberg and co-workers[7] have reported LH dynamics following progesterone injection, showing a stimulation of LH output in patients who subsequently responded with ovulation to clomiphene administration, and Mishell and Odell[8] reported increased LH levels after administration of the potent progestational agent ethynodiol diacetate. Endometrial bleeding ordinarily occurs 3 to 7 days after discontinuing therapy with a progestational agent. Although the span from LH increase to bleeding in Group B patients ranged from 8 to 16 days, bleeding always occurred less than 6 days after discontinuing Danazol, even when the drug was only given for 5 days. In Cycles II and IV, Patient L. M. received progesterone suppositories which obviously delayed the bleeding.

The mechanism of action of Danazol in the therapy of cystic mastitis, precocious puberty, and endometriosis becomes rational if Danazol acts as a progestational agent. The appearance of an atrophic endometrium after chronic dosage, and the irregular spotting frequently observed during early treatment probably represent the spectrum of effect of a progestational agent. Its contraceptive action is probably based on the same mechanism.

Finally, Creange and Potts[9] have reported that, of known Danazol metabolites, 2-hydroxymethyl ethisterone may be present in human plasma in amounts five to 10 times that of Danazol. Therefore, the possibility that a Danazol metabolite may be exerting the progestational activity cannot be overlooked, but with present knowledge, cannot be proved.

Danazol was supplied by the Sterling-Winthrop Research Institute, Rensselaer, New York. Materials for radioimmunoassay of FSH and LH were generously supplied by the Endocrinology Study Section, National Institutes of Health, and the assays were run by Barbara Widerman. The authors thank Kathy Wieman for the drawings and Lois Williams for secretarial assistance.

Addendum

Recent unpublished observations have indicated that Danazol administration to the estrogen treated, castrated rhesus monkey has induced no progestational change (personal communication, Dr. G. O. Potts). Furthermore, the Danazol metabolite, 2-hydroxymethyl ethisterone, has been shown to be biologically inert.

REFERENCES

1. Dmowski, W. P., Scholer, H. F. L., Mahesh, V. B., and Greenblatt, R. B.: Danazol—A synthetic steroid derivative with interesting physiologic properties, Fertil. Steril. **22:** 9, 1971.
2. Potts, G. O., Beyler, A. L., and Schane, H. P.: Pituitary gonadotropin inhibitory activity of Danazol, Fertil. Steril. **25:** 367, 1974.
3. Greenblatt, R. B., Dmowski, W. P., Mahesh, V. B., and

Scholer, H. F. L.: Clinical studies with an antigonadotropin—Danazol, Fertil. Steril. **22:** 102, 1971.
4. Andrews, M. C., and Wentz, A. C.: The effects of Danazol on gonadotropins and steroid blood levels in normal and anovulatory women, AM. J. OBSTET. GYNECOL. **121:** 817, 1975.
5. Wood, G. P., Wu, C. H., Flickinger, G. L., and Mikhail, G.: Hormonal changes associated with Danazol therapy, Obstet. Gynecol. **45:** 302, 1975.
6. Noyes, R. W., Hertig, A. T., and Rock, J.: Dating the endometrial biopsy, Fertil. Steril. **1:** 3, 1950.
7. Goldenberg, R. L., Grodin, J. M., Vaitukaitis, J. L., and Ross, G. T.: Withdrawal bleeding and luteinizing hormone secretion following progesterone in women with amenorrhea, AM. J. OBSTET. GYNECOL. **115:** 193, 1973.
8. Mishell, D. R., and Odell, W. D.: Effect of varying dosages of ethynodiol diacetate upon serum luteinizing hormone, AM. J. OBSTET. GYNECOL. **109:** 140, 1971.
9. Creange, J. E., and Potts, G. O.: A competitive radioligand assay for Danazol (17$^{\alpha}$-pregn-4-en-20yno [2,3-d] isoxazol-17-ol) using pregnant guinea pig plasma, Steroids **23:** 411, 1974.

The effect of prophylactic ampicillin on pelvic infection following vaginal hysterectomy

M. W. GLOVER, M.D.

J. R. VAN NAGELL, JR., M.D.

Lexington, Kentucky

One hundred patients undergoing vaginal hysterectomy at the University of Kentucky Medical Center were given prophylactic ampicillin and compared to one hundred control patients. The use of prophylactic ampicillin caused significant reduction in both postoperative pelvic infection and hospital stay. However, two patients in the prophylactic antibiotic group later required readmission for infections resistant to ampicillin. Prophylactic antibiotics are beneficial in vaginal hysterectomy, but careful follow-up of all patients is mandatory.

WITH THE INCREASING costs of medical care, much attention has been directed toward measures to reduce the duration of hospital stay following operation. One such measure is the use of prophylactic antibiotics before, during, and after major operative procedures. Although initial studies in patients undergoing bowel operation showed no particular benefits from the use of prophylactic antibiotics,[1, 2] more recent investigations in gynecologic surgery[3, 4, 7] have indicated that prophylactic antibiotics can significantly reduce postoperative morbidity and hospital stay.

Vaginal hysterectomy is an excellent procedure in which to evaluate the effect of prophylactic antibiotics for two reasons. First, vaginal hysterectomy is performed through a bacterially contaminated field. Ledger and colleagues[3] were able to recover bacteria from the vaginal cuff after removal of the uterus in over 95 per cent of patients. Likewise, Gorbach and co-workers[5] cultured both aerobes and anaerobes from the external cervix in over 70 per cent of healthy premenopausal women. Second, vaginal hysterectomy is associated with a high incidence of operative-site infection. Allen and colleagues[6] reported a 38 per cent incidence of pelvic cellulitis or abscess after vaginal hysterectomy when prophylactic antibiotics were not used. Similarly, Goosenberg and associates[7] noted that febrile morbidity occurred in 31 of 40 patients (77.5 per cent) following vaginal hysterectomy without antibiotics.

The present investigation was undertaken to determine the effect of prophylactic ampicillin on febrile morbidity and hospital stay following vaginal hysterectomy. In addition, an attempt was made to ascertain if there were any delayed complications following hospitalization related to the use of this antibiotic.

Material and methods

From July 1, 1971, to June 30, 1975, vaginal hysterectomy was performed on 300 patients at the University of Kentucky Medical Center as part of a prospective study to evaluate the effect of prophylactic antibiotics on postoperative pelvic infection. No patient undergoing anterior or posterior vaginal repair was included in this study.

A Furacin* suppository was placed in the vagina 12 hours prior to hysterectomy. Immediately before operation, the perineum and vagina were scrubbed with pHisoHex-iodine† solution. Vaginal hysterectomy was performed according to the Heaney technique in all patients, and the duration of operation was recorded. A Foley catheter was placed in the bladder following completion of operation and was removed on the first

From the Department of Obstetrics and Gynecology, University of Kentucky Medical Center.

Received for publication October 21, 1975.

Revised February 16, 1976.

Accepted April 7, 1976.

Reprint requests: Dr. J. R. van Nagell, Jr., Department of Obstetrics and Gynecology, University of Kentucky Medical Center, Lexington, Kentucky 40506.

*Eaton Labs., Inc., Div. Norwich Pharm. Co., 17 Eaton Ave., Norwich, New York 13815.

†Winthrop Labs., Div. of Sterling Drug Inc., 90 Park Ave., New York, New York 10016.

Table I. Clinical characteristics of patients

Characteristic	*No antibiotics*	*Penicillin and streptomycin*	*Ampicillin*
No. of patients	100	100	100
Mean age (years)	31.2	30.7	27.9
Mean gravidity	4.7	4.7	4.1
Mean parity	4.2	4.1	3.6

Table II. Indications for vaginal hysterectomy

Indication	*No antibiotics*	*Penicillin and streptomycin*	*Ampicillin*
Multiparity	49	49	60
Carcinoma in situ or microinvasion	39	37	30
Severe dysplasia	5	5	6
Abnormal uterine bleeding	4	4	3
Pelvic relaxation or prolapse	3	3	1
Other	0	2	0
Total patients	100	100	100

Table III. Duration of operation, estimated blood loss, morbidity, and postoperative hospitalization

	No antibiotics	*Penicillin and streptomycin*	*Ampicillin*
Mean duration of operation (min.)	62	61	60
Mean estimated blood loss (ml.)	302	282	242
Bleeding requiring transfusion (patients)	3	5	2
Mean postoperative hospital stay (days)	6.3	5.0	5.6

postoperative day. Blood loss was estimated by sponge weight plus the recorded volume present in the suction bottle at the end of the procedure.

One hundred patients received no antibiotics; one hundred patients were given prophylactic penicillin and streptomycin, and one hundred patients received prophylactic ampicillin. The details of drug administration and results obtained with prophylactic penicillin and streptomycin have been previously reported.[8] The present investigation will deal primarily with those patients who received prophylactic ampicillin. Ampicillin was administered according to the following protocol: 0.5 Gm. orally 12 and six hours prior to operation and 0.5 Gm. intravenously at the time of operation and every six hours thereafter for a total of four doses. The total dose of ampicillin given to each patient was 3 Gm. No patient in this group was allergic to penicillin.

Febrile morbidity was defined as a temperature of 100.4° F. or greater on two occasions separated by at least six hours after the first 24 hours following operation. Aerobic and anaerobic cultures with the use of both thioglycollate and laked blood agar culture media were taken from the urine and vaginal cuff in all patients with febrile morbidity or in whom there were clinical signs of pelvic infection. Urinary tract infection was defined as a bacterial colony count of more than 100,000 per milliliter obtained from a urethral catheter or a clean voided specimen. Pelvic cellulitis was diagnosed when there was pelvic induration and purulent drainage from the vaginal cuff in the absence of a pelvic mass. Technical morbidity was defined as febrile morbidity, the etiology of which could not be established.

All patients were seen two and six weeks following operation as well as at any time during which signs of pelvic infection developed.

Results

The clinical characteristics of the patients studied are presented in Table I. The age and reproductive status were not significantly different in any of the three groups. Likewise, the indications for operation (Table II) were similar in all patients, with multiparity and intraepithelial carcinoma being the most common indications cited. The mean blood loss and transfusion rate were slightly reduced in those patients receiving prophylactic ampicillin (Table III). However, operative time was identical in all three groups. Febrile morbidity was significantly ($p < 0.001$) reduced in those patients receiving prophylactic ampicillin when compared to the control group. Specifically, the incidence of pelvic infection (cellulitis or abscess) was reduced from 18 to 3 per cent ($p < 0.01$) with the use of prophylactic ampicillin (Table IV).

The most common infecting organisms in the control group were *E. coli* and *S. faecalis,* which were cultured from the vaginal cuff in 13 patients and from the urine in five patients (Table V). These organisms were responsible for pelvic or urinary tract infections in only two patients in the prophylactic ampicillin group. The types of infecting organisms did not differ significantly in those patients receiving the two different prophylactic antibiotics. One patient who was given ampicillin developed a vaginal cuff abscess secondary to coagulase-positive *Staphylococcus aureus* which was resistant

Table IV. Etiology of febrile morbidity

Diagnosis	*No antibiotics*	*Penicillin and streptomycin*	*Ampicillin*
Vaginal cuff cellulitis	18	1	2
Urinary tract infection	6	2	1
Atelectasis	6	1	0
Technical	5	4	1
Pelvic thrombophlebitis	1	0	0
Vaginal cuff abscess	1	0	1
Thrombophlebitis of lower extremity	0	0	1
Total (%)	37	8	6

Table V. Culture results

Results	*No antibiotics*	*Penicillin and streptomycin*	*Ampicillin*
Vaginal cuff cellulitis or abscess organisms)			
Escherichia coli	8	0	2
Streptococcus faecalis	5	0	0
Proteus mirabilis	1	0	0
Group B beta streptococcus	1	0	0
Diphtheroids	1	0	0
Staphylococcus aureus, coagulase positive	0	0	1
No growth	1	1	3
Urinary tract infection (organisms)			
Escherichia coli	4	2	1
Streptococcus faecalis	1	0	0
Group B beta streptococcus	1	0	0

to ampicillin. This infection responded to treatment with oxacillin, but the patient had a prolonged postoperative hospital stay of 13 days. Likewise, one patient developed superficial thrombophlebitis of the left lower extremity which was treated with intravenous heparin. There were no allergic reactions to ampicillin and no complications related to its administration.

Two patients in the prophylactic ampicillin group required readmission to the hospital for pelvic infections. One patient developed pelvic cellulitis and a purulent vaginal discharge on the eighteenth postoperative day. Culture of the vaginal cuff revealed *E. coli* which was resistant to ampicillin. This infection responded satisfactorily to a seven-day course of Kanamycin. The second patient was admitted eight days following hysterectomy with a right ovarian abscess which grew the Fusobacterium species and necessitated salpingo-oophorectomy. It is important to note that both of these patients had a completely normal initial postoperative course and were discharged from the hospital afebrile and asymptomatic five days after hysterectomy.

Comment

With several recent studies showing a beneficial effect of prophylactic antibiotics in patients undergoing pelvic operation,[3, 4, 6–9] it is imperative that prophylactic antibiotics not be used indiscriminantly. Serious complications and even death have been attributed to the use of prophylactic antibiotics.[10] Ledger and co-workers,[3] in an excellent review of the etiology and treatment of pelvic infections following gynecologic operation, proposed several guidelines for the proper use of prophylactic antibiotics. Included in these guidelines were the recommendations that prophylactic antibiotics be started prior to operation and that they be used only in those surgical procedures associated with a high incidence of operative-site infection. The findings of the present study confirm these observations and demonstrate the efficacy of prophylactic antibiotics in vaginal hysterectomy. Pelvic infection was significantly decreased and hospital stay was reduced in those patients receiving prophylactic antibiotics.

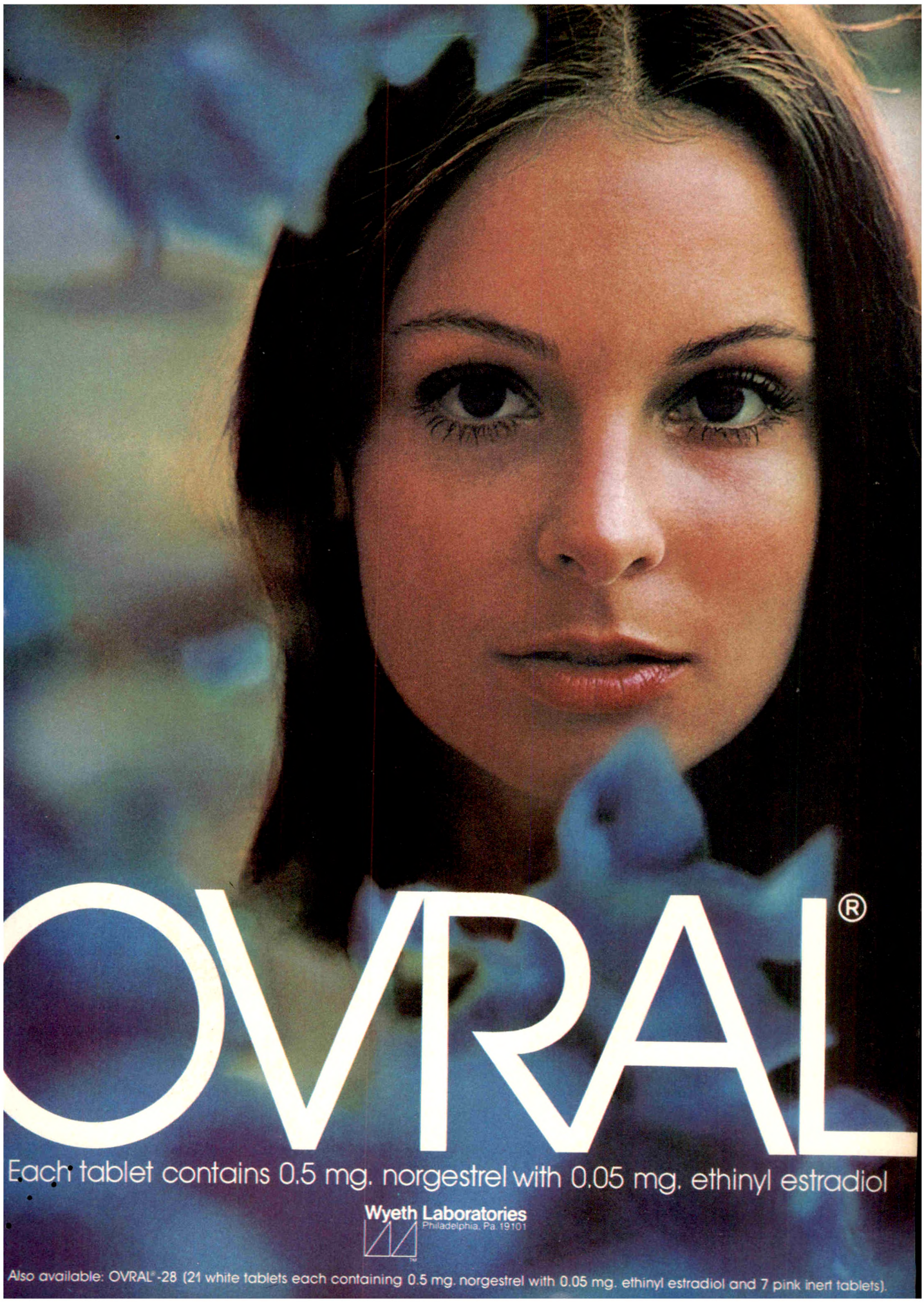
Although this was not a double-blind study, the patient population, institution, and surgical technique were identical in all patients. Ampicillin reduced the rate of pelvic infection to approximately the same level as that observed with the combination of penicillin and streptomycin, and the organisms cultured from those patients who developed pelvic infections while receiving prophylactic antibiotics were similar in both groups.

Perhaps the most significant observation of the present investigation was that two patients in the prophylactic ampicillin group who had a benign initial posthysterectomy course required readmission for a pelvic infection secondary to an organism which was resistant to ampicillin. It is difficult to conclude that prophylactic antibiotics actually contributed to these delayed infections. However, this does emphasize the need for careful follow-up of all patients following hysterectomy, whether or not prophylactic antibiotics have been used.

The data from this and other investigations[3, 4, 6–8] support the concept that prophylactic antibiotics are beneficial in vaginal hysterectomy. Their use should in no way preclude careful surgical technique or adequate postoperative follow-up.

REFERENCES

1. McKittrick, L. S., and Wheelock, F. C.: The routine use of antibiotics in elective abdominal surgery, Surg. Gynecol. Obstet. **99:** 376, 1954.
2. Johnstone, F. R.: An assessment of antibiotics in general surgery, Surg. Gynecol. Obstet. **116:** 1, 1963.
3. Ledger, W. J., Gee, C., and Lewis, W. P.: Guidelines for antibiotic prophylaxis in gynecology, Am. J. Obstet. Gynecol. **121:** 1038, 1975.
4. Ledger, W. J., Sweet, R. L., and Headington, J. T.: Prophylactic cephaloridine in the prevention of postoperative pelvic infections in premenopausal women undergoing vaginal hysterectomy, Am. J. Obstet. Gynecol. **115:** 766, 1973.
5. Gorbach, S. L., Menda, K. B., Thadepalli, H., and Keith, L.: Anaerobic microflora of the cervix in healthy women, Am. J. Obstet. Gynecol. **117:** 1053, 1973.
6. Allen, J. L., Rampone, J. F., and Wheeless, C. R.: Use of a prophylactic antibiotic in elective major gynecologic operations, Obstet. Gynecol. **39:** 218, 1972.
7. Goosenberg, J., Emich, J. P., and Schwarz, R. H.: Prophylactic antibiotics in vaginal hysterectomy, Am. J. Obstet. Gynecol. **105:** 503, 1969.
8. Harralson, J. D., van Nagell, J. R., Jr., Roddick, J. W., Jr., and Sprague, A. D.: The effect of prophylactic antibiotics on pelvic infection following vaginal hysterectomy, Am. J. Obstet. Gynecol. **120:** 1046, 1974.
9. Bolling, D. R., Jr., and Plunkett, G. D.: Prophylactic antibiotics for vaginal hysterectomies, Obstet. Gynecol. **41:** 689, 1973.
10. Ledger, W. J., and Puttler, O. L.: Death from pseudomembranous enterocolitis, Obstet. Gynecol. **45:** 609, 1975.
11. Rosenheim, G. E.: Prophylactic antibiotics in elective abdominal hysterectomy, Am. J. Obstet. Gynecol. **119:** 335, 1974.


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol
Wyeth Laboratories
Philadelphia, Pa. 19101
Also available: OVRAL®-28 (21 white tablets each containing 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol and 7 pink inert tablets).



Estrogen as natural to her body as the estrone it restores

OGEN®
(PIPERAZINE ESTRONE SULFATE)

Helps you arrive at the minimum estrogen dosage needed to relieve her symptoms



One Divide-Tab® tablet may well be the correct dosage but only trial can tell.



Some patients may require only half this dosage for relief of symptoms.



Other patients may experience partial relief of symptoms when a half-tablet more would provide complete control.

In short: Divide-Tab tablets help you determine how much is needed and how little is enough . . . with one prescription.

6053143

See following page for Brief Summary.

ABBOTT

OGEN® PIPERAZINE ESTRONE SULFATE

offers you four Divide-Tab® dosage strengths for greater flexibility



OGEN .625
(piperazine estrone sulfate 0.75 mg., calculated as sodium estrone sulfate 0.625 mg.)



OGEN 1.25
(piperazine estrone sulfate 1.5 mg., calculated as sodium estrone sulfate 1.25 mg.)



OGEN 2.5
(piperazine estrone sulfate 3 mg., calculated as sodium estrone sulfate 2.5 mg.)



OGEN 5
(piperazine estrone sulfate 6 mg., calculated as sodium estrone sulfate 5 mg.)

6053143R1

Brief Summary

Important Notes: It has now been conclusively established that the use of oral contraceptives containing estrogens and progestins is associated with an increased risk of thromboembolic disease. Retrospective studies have shown a statistically significant association between the use of these drugs and thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism. This conclusion is based on three principal studies[1-3] done in Great Britain and one[4] done in the U.S. Based on these studies it has been estimated that users of oral contraceptives are four to seven times more likely than nonusers to develop thromboembolic disease with no evident cause. The American study also indicated that the increased risk did not persist after the drug was discontinued, nor was it enhanced by long-term administration. Although this study was not designed to evaluate a difference between products, the results suggested that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis[5] of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen in the oral contraceptive used. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles to use the smallest effective dose of estrogen in treating patients, whenever feasible.

The degree of risk associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate has not yet been satisfactorily determined.

Long-term administration of both natural and synthetic estrogens in multiples of the human dose to subprimate animal species increases the frequency of some animal carcinomas. Conclusions based on these data cannot be applied directly to man. The possible carcinogenicity of the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued.

It has been reported in a recent study[6] done in the United States that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of the development of vaginal adenocarcinoma years later in the exposed offspring.

Indications: OGEN (piperazine estrone sulfate tablets) is indicated:—For replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure. In the management of senile vaginitis; in kraurosis vulvae with or without pruritus.

For the prevention of postpartum breast engorgement.

In the management of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

In inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: Estrogens are contraindicated in patients with known or suspected carcinoma of the breast, except in those cases of progressive disease not amenable to surgery or irradiation occurring in women who are at least five years postmenopausal or in men in whom castration is not feasible. They are also contraindicated in patients with other known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium.

These drugs are further contraindicated in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions, in patients with markedly impaired liver function, and in those with undiagnosed, abnormal genital bleeding.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected, the drug should be discontinued immediately. If there is a sudden onset of proptosis, diplopia, or migraine, the medication should be discontinued pending an examination. If papilledema or retinal vascular lesions are found, the medication should be withdrawn.

Estrogens may be excreted in the mother's milk, and an estrogenic effect upon the nursing infant has been described. The long range effect on the infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This effect is not dependent on dose or immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Precautions: Because normal endogenous hormone production varies among individuals, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, or other effects (see ADVERSE REACTIONS).

Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

If any unexplained or excessive vaginal bleeding occurs during estrogen therapy, nonfunctional causes should be considered. The drug should be discontinued and a thorough investigation made of the cause, being certain to ascertain that a malignancy is not present.

Pre-existing uterine fibromyomata may increase in size with estrogen therapy; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

A pre-treatment physical examination should include special attention to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. Estrogens should be used cautiously in women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast.

To avoid this, oral estrogens should be administered cyclically to the menopausal or hypogonadal patient.

Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Estrogens influence the metabolism of calcium and phosphorus and should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is not complete. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Urinary stress incontinence may occur when large doses of estrogens are used in nonpregnant women.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient receiving an estrogen, it is recommended that they be repeated after the drug has been withheld for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function will require further study.

Adverse Reactions: Although not all of the following reactions have been specifically associated with OGEN (piperazine estrone sulfate tablets), they have been reported with estrogens generally and may be encountered when giving any estrogen.

Gastrointestinal: nausea, anorexia, vomiting, abdominal cramps, bloating, cholestatic jaundice and increase or decrease in body weight.

Genitourinary: sodium and water retention, breakthrough bleeding, spotting, and withdrawal bleeding, increased cervical mucus, reactivation of endometriosis, and cystitis-like syndrome.

Endocrine: breast swelling and tenderness, possible diminution of lactation when given immediately postpartum, increased blood sugar levels, and decreased glucose tolerance.

Central Nervous System: headaches, mental depression, increase or decrease of libido, nervousness, dizziness, fatigue irritability and malaise.

Dermatologic-Hypersensitivity: loss of scalp hair, allergic reactions and rashes, hemorrhagic eruption, itching, erythema nodosum, and erythema multiforme.

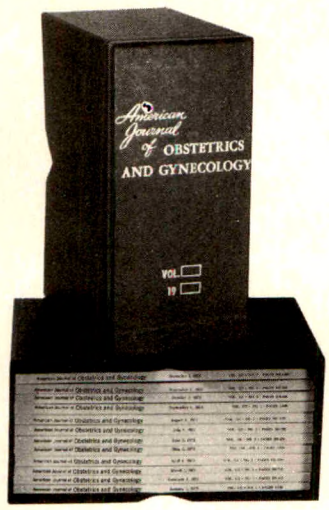
Musculoskeletal: backache.

Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches.

Hematologic: a statistically significant association has been demonstrated between the use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuroocular lesions (e.g., retinal thrombosis and optic neuritis).

Miscellaneous: premenstrual-like syndrome and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

ABBOTT



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼" × 11") for 1975 copies
☐ OLD SIZE (7¼" × 10½") for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

dialogue in fetal monitoring

This is the first in a series of educational seminars designed with the purpose of maintaining an international dialogue among members of the obstetrical community. The 2-1/2 day program will cover clinical aspects of today's fetal monitoring as well as changes and trends in obstetrical care. Discussions and lectures by prominent guest speakers from both the United States and Europe will afford an excellent opportunity to exchange ideas and compare philosophies and techniques.

The co-chairmen of this educational event are Dr. Richard Depp of Northwestern University and Dr. Helge Ruettgers of Heidelberg University. We hope you will plan to join us

NOVEMBER 11 – 13, 1976
at the New Orleans Marriott Hotel.

Registration fee is $185. For further information please call or write:

Hewlett-Packard Company
175 Wyman Street, Waltham, Mass. 02154
Tel: (617) 890-6300
Jane Fredriksen, Seminar Coordinator

This course has been approved for 25 cognates by the American College of Obstetricians and Gynecologists. Attendance will be limited to 250 participants.

sponsored by

HEWLETT hp PACKARD

Perinatal Education Department

Upjohn

Microbiologic aspects of fertility...

The greatest potential for bacterial infection in the female genital tract exists during the fertile years. A large proportion of the potentially pathogenic microflora are anaerobic—particularly bacteroides and anaerobic streptococci. Isolation and identification present special problems.

"Pseudo-maturity"

Sterile at the time of birth, the female genitalia begin to develop an abundant bacterial flora within hours. But this maternally influenced flora, composed largely of the familiar gram-positive lactobacillus known as Döderlein's bacillus, disappears in just a few weeks. The vaginal secretions revert toward alkalinity and remain alkaline until puberty. A varied flora of staphylococci, streptococci (except pyogenes), coliforms and diphtheroid bacilli is present.

The healthy mature female

With the onset of menstruation, conditions within the vagina change appreciably. For example, the glycogen content of the vaginal epithelium is markedly increased under the influence of ovarian hormones. This, in turn, encourages the proliferation of Döderlein's bacilli. These lactobacilli create an acid environment which limits the growth of potential pathogens, and the role of lactobacilli in keeping the microflora in balance is vital throughout a woman's reproductive years.

The normal flora—anaerobes predominate Certain other bacteria are also seen regularly in the vagina. With today's improved methods of culturing, it has been demonstrated that a large proportion of these bacteria are anaerobic—notably bacteroides and anaerobic streptococci. Other microorganisms that may be observed are the *Escherichia coli/Enterobacter aerogenes* group of coliforms, the anaerobic micrococci, group B streptococci, enterococci, diphtheroids, and *Hemophilus vaginalis*. The presence of any of these microorganisms may or may not be a matter of etiologic importance.

Disturbing influences—balance upset Not all gynecologic infections are of endogenous origin. Changes in hormonal balance—for example, during pregnancy—nearly always influence the microbiological balance. Both



he resident bacterial population and potential invading pathogens may be affected. Either may be responsible for the occurrence of postpartum infections, postabortal infections, posthysterectomy infections, and the infections that occur concurrently with neoplastic disease. As pathogens ascend the reproductive tract from vagina to uterus to tubes, the risk to the patient is usually enhanced.

Forms of infection

Gynecologists and surgeons alike are well acquainted with such infections: abscesses (whether tuboovarian, pelvic, vaginal, vulval, or Bartholin's gland infection), puerperal sepsis, salpingitis, endometritis, peritonitis of gynecologic origin, vaginal-cuff infection, chronic pelvic inflammatory disease—with each, the threat of possible septicemia. The need for immediate surgical intervention may be controversial, but certain of these infections often represent true gynecologic emergencies.

The problems anaerobes pose...culturing

Improved culturing techniques have demonstrated that anaerobes—especially bacteroides and anaerobic streptococci—inhabit the vagina, as well as more remote genital areas. It has been reported that these usually foul-odor-producing anaerobic organisms may be isolated in three out of four cases of infections of the genital tract. In one series of patients, anaerobes alone were cultured in 37 percent of the cases. Many studies have shown that bacteroides are by far the most common of these organisms, but anaerobes such as peptococci, peptostreptococci and other anaerobic streptococci are also frequently observed. Mixed infections with multiple anaerobic species are not unusual.

Today many physicians suspect that the techniques of obtaining or incubating the culture may be at fault if no anaerobes at all are observed.

A new appreciation of pathogenicity

Only recently has it been realized that anaerobes other than clostridia are pathogens of major significance in serious infections of the female genital tract. Exacting methods of culturing have helped to establish this. One investigation has shown that 44 percent of all anaerobic isolates obtained from a series of 400 patients of all types, not just gynecologic, were associated with infection. Bacteroides and anaerobic streptococci were the most prevalent, with clostridia occurring less frequently.

Whenever these organisms are seen on repeated occasions by Gram stain or isolated by culture—whether alone or combined with other bacteria—they should not be ignored.

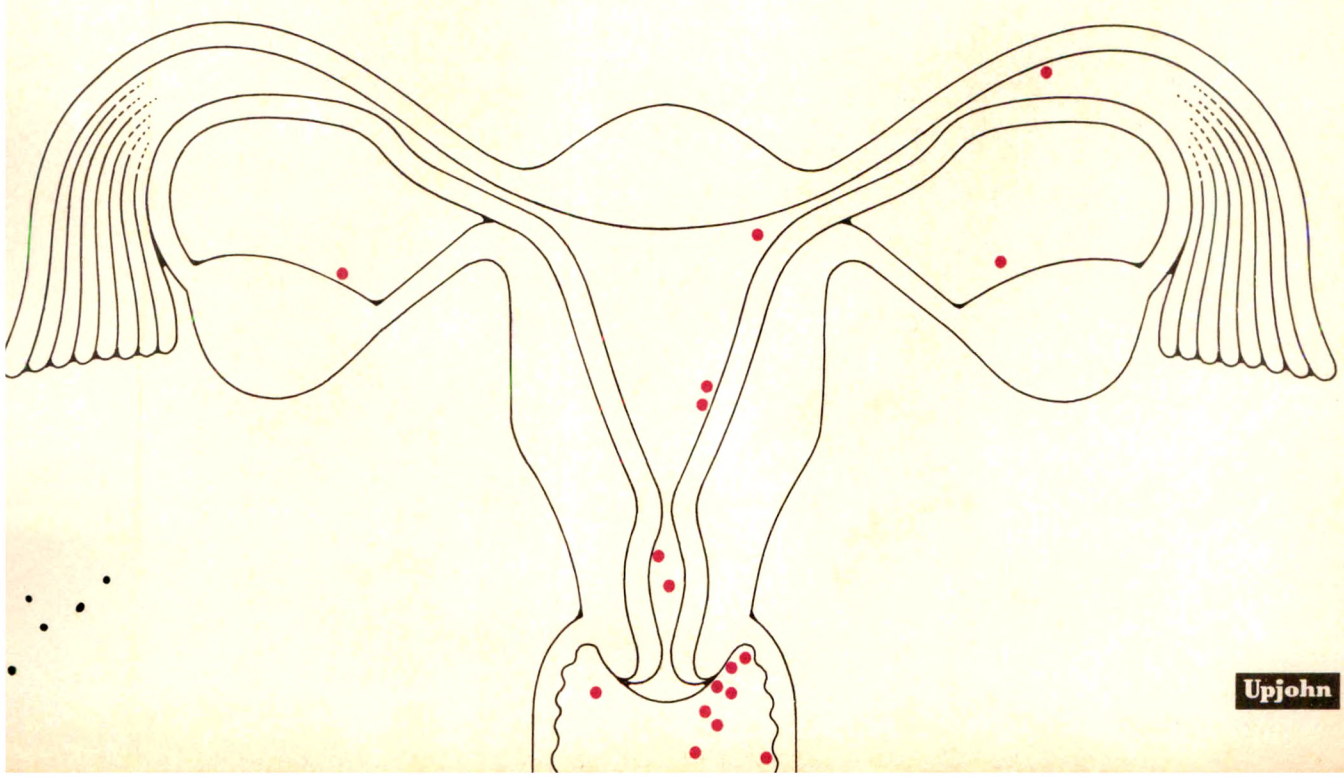
Therapeutic measures

Selection of the most appropriate antibiotic—or antibiotics—is still a problem for the gynecologist in many instances, since many of the infections he deals with cannot be etiologically defined when first observed. Nevertheless, the seriousness of his patient's condition may demand immediate attention. Because there are numerous antibiotics effective against just certain potential pathogens, the physician's problem has been intensified. And for one aspect of his problem—anaerobic infections—there has been no easy answer.

Many gynecologists believe that, of all infections, these present one of today's most serious challenges.

For information on ONE ANTIBIOTIC OF SIGNIFICANCE in the treatment of serious anaerobic infections of the female reproductive tract, please turn page.

©1975 THE UPJOHN COMPANY



Upjohn

Upjohn

Therapeutic considerations...

Cleocin® Phosphate (clindamycin phosphate injection) has proved to be effective against susceptible anaerobic organisms (whether they are anaerobic cocci or anaerobic gram-positive or gram-negative rods). Specifically its activity has been established in serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, peptococci, peptostreptococci, microaerophilic streptococci, or clostridia.* Furthermore, Cleocin PO_4 has proved successful in septicemia and in such nongynecologic conditions as serious intra-abdominal infections (peritonitis, intra-abdominal abscess), serious respiratory-tract infections (empyema, anaerobic pneumonitis, lung abscess), and serious infections of skin and soft-tissue caused by susceptible anaerobic organisms.

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious gram-positive infections The use of Cleocin PO_4 in serious nongynecologic infections caused by susceptible gram-positive organisms has been extensively investigated both bacteriologically and clinically. Because Cleocin PO_4 is a parenteral antibiotic, emphasis has been on evaluation of the drug in serious infections, and the appropriate patients for Cleocin PO_4 are those who are hospitalized with serious illnesses.

Diagnoses have included septicemia and septic shock, acute peritonitis, staphylococcal pneumonia, and massive wound infection. In many cases the infection was secondary to severe accidental trauma, major surgery, or debilitating disease.

Cleocin PO_4 has produced excellent results when the pathogens in these serious infections proved to be staphylococci, streptococci (except enterococci), or pneumococci. With rare exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions, regardless of the severity of the infection. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Other therapeutic considerations:

1) Cleocin PO_4 is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.
2) Cleocin is useful in patients who are sensitive to penicillin. Rare cases of sensitivity to Cleocin resulting in maculopapular rash and urticaria have been reported; as with all antibiotics, it should be used cautiously in atopic patients. Serious anaphylactoid reactions require emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated. However, no actual cross-antigenicity with other antibiotics has been demonstrated, *except with lincomycin.*

Because of these two benefits, Cleocin PO_4 can fill a need both for penicillin-sensitive patients and those harboring penicillin-resistant organisms.



Cleocin PO_4 should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

WARNINGS: (See WARNING box on following page.)

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.

Safety for use in pregnancy has not been established.

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g., *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to. . . . . 150 mg clindamycin base

benzyl alcohol. . . . . 5 mg

disodium edetate. . . . . 0.5 mg

water for injection. . . . . qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

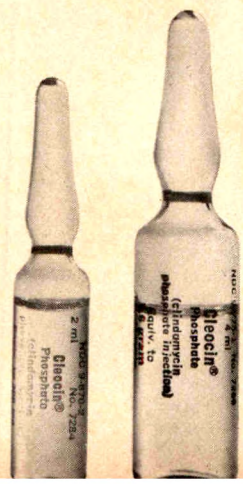
Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.



Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of non-susceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED B-4-S (NFM-3) J-4919-9

STERILE SOLUTION

Cleocin PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001



She's looking to you for answers. Reassure her.

Results of ten years' clinical experience with Saf-T-Coil® can help you provide the information she's seeking.

Saf-T-Coil is an IUD found comparable to the "pill" in use effectiveness.[1-3] Results of one of the longest investigations—a five-year study[2] in Florida clinics, based on 27,712 insertions and 541,248 woman-months of use—indicate: a low 0.8% *in situ* pregnancy rate, high 80% continuation rate, 11.9% expulsion rate and 8.0% removal rate. Subsequently, the investigators made Saf-T-Coil their "device of first choice."

Three Saf-T-Coil sizes ensure contraceptive effectiveness throughout her reproductive years: Saf-T-Coil Nullip 25-S for the nulliparous and young woman, Saf-T-Coil 32-S for the primiparous woman and Saf-T-Coil 33-S for the multiparous woman.

Saf-T-Coil Nullip 25-S, in particular, has proved to be a device well-suited to the woman with a small uterus. Results of a separate two-year study[1] in Florida clinics, based on 1,179 insertions and 9,750 woman-months of use, indicate a low 0.4% *in situ* pregnancy rate, relatively high 70% continuation rate, 11% expulsion rate and 19% removal rate—both considered acceptable in nulliparous patients. Insertions were easy and virtually painless, using the standard techniques and no anesthesia. And the Nullip 25-S rapidly accommodated to the shape of the uterine cavity—in contrast to the more rigidly designed devices,which force the uterus to conform. No serious complications were reported in this study.

Every Saf-T-Coil is made of inert plastic with no copper additives.

And with every Saf-T-Coil—Saf-T-Sound®—the sterile, disposable intrauterine probe that helps make fitting easier and more accurate.

Caution: Federal law restricts this product to sale by or on the order of a physician.
Contraindications: Should not be used in pregnancy or suspicion of pregnancy, suspicion of carcinoma, acute cervicitis, acute or subacute adnexal disease, fibroids, menorrhagia or unexplained bleeding.

1. Caraway, A. F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A. F. and Vaughn, B. J.: J. Reprod. Med. *10*:171, April 1973.
3. Hayes, O. J.: South. Med. J. *66*:254, Feb. 1973.

Sterile, inert plastic

Saf-T-Coil®

SCHMID LABORATORIES, INC.
LITTLE FALLS, NEW JERSEY 07424

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

The treatment of cystocele and uterine prolapse after the menopause

THOMAS JAMES WATKINS

American Gynecological and Obstetrical Journal, vol. 15, pp. 420-423 and 437, 1899

dated her illness from birth of last child, which occurred 22 years before. Her suffering had increased since the menopause, which occurred four years previously. She suffered much distress from "bearing-down" pains, backache, and pain in the inguinal regions on walking and standing. A protrusion at the vulvar orifice mechanically interfered with walking and sitting. She also suffered from leucorrhœa and vesical irritability. Examination revealed a large cystocele and rectocele. The uterus was atrophied, retroverted, and prolapsed to the second degree.

An operation was made January 29, 1898, as follows: After the usual preparations, the uterus was curetted and separated from the vagina by a circular incision. The bladder was separated from the uterus by blunt dissection and the peritonæal cavity opened in front of the uterus. The anterior wall of the uterus was grasped by bullet forceps and the organ anteverted. About two inches of the upper portion of the anterior vaginal wall was excised. The anterior vaginal wall was now sutured to the upper border of the broad ligaments lateral to the uterus, and to the fundus of the uterus with silkworm-gut sutures. The posterior vaginal wall was incised, longitudinally in the medium line from the cervix downward, about one inch so as to allow the cervix to be displaced upward and backward. The wound in front of the cervix was now closed by silkworm-gut sutures inserted transversely, that is, parallel to the line of incision anterior to the cervix. The operation had at this stage lengthened the anterior vaginal wall, obliterated the cystocele, and forced the cervix upward and backward into its normal location. One silkworm-gut suture secured the cervix in the angle of the incision in the posterior vaginal wall. Emmet's perineorrhaphy was made to correct the prolapse and displacement of the posterior vaginal wall. The sutures were removed at the end of four weeks when the union was found to be perfect. The vagina was about normal length, the uterus anteverted and the vaginal walls free from prolapse.

The result was much better than any I have seen follow other operations for like conditions. The patient suffered no more that is usual after plastic vaginal operation. She has continued to be entirely free from pelvic distress.

This operation is an application of the principles of the operation of vaginal fixation for retroposition of the uterus. The operation differs from the usual vaginal-fixation operation in excision of enough of the anterior vaginal wall to obliterate the cystocele after the sutures are inserted and tied; in suturing the anterior vaginal wall to the broad liga-

During the latter part of the nineteenth century, several gynecologists experimented with techniques for the correction of uterine prolapse associated with cystocele. European surgeons including A. Dührrsen, A. K., Mackenrodt, W. A. Freund, and H. Fritsch developed procedures to vaginally fix retroposition of the uterus. E. Wertheim described an interposition operation with the uterus used to support the bladder (Zentralbl. Gynaekol. 23: 369, 1899). However, Watkins, of Chicago, first described the interposition operation as we know it today. He first performed the procedure on a 58-year-old woman (see illustration). In a later report (Surg. Gynecol. Obstet. 2: 659, 1906), he outlined the principles of the operation: "1) The bladder is supported by and rests upon the posterior wall of the uterus. 2) The uterus is elevated in the pelvis by being tipped forward, in fact, its position is changed about 180°. The twist produced in the broad ligaments by the change in the position of the uterus perceptibly shortens them. This twisting of the broad ligaments is the chief factor in correcting the uterine prolapse. 3) The tendency for the uterus and bladder to prolapse, following the operation, are antagonistic, as any sagging of the bladder increases the anterior displacement of the uterus, and any prolapse of the uterus elevates the bladder wall." Subsequent workers amputated the cervix in an effort to remove a potential site of disease. Mainly because of the inaccessibility of the endometrial cavity in cases of postmenopausal bleeding, the Watkins interposition has been replaced by the Manchester operation of vaginal hysterectomy with anterior and posterior colporrhaphy.

CURRENT DEVELOPMENTS

Mercury toxicity in the pregnant woman, fetus, and newborn infant

A review

BRIAN J. KOOS, M.D.
LAWRENCE D. LONGO, M.D.
Loma Linda, California

This paper reviews the reported cases of mercury poisoning in pregnancy and the data based on sources of contamination, maternal uptake, and distribution. It analyzes current knowledge of placental transfer of various mercury compounds, fetal uptake, and distribution. It identifies the embryopathic and fetal toxic effects of mercury in general while emphasizing the greater toxicity of methylmercury compounds. Since maternal exposure to methylmercury is primarily through fish consumption, it recommends that women of childbearing age should not consume more than 350 Gm. of fish per week. In addition, they should not be occupationally exposed to air concentrations of mercury vapor greater than 0.01 mg. per cubic meter, of inorganic and phenylmercuric compounds greater than 0.02 mg. per cubic meter, or any detectable concentration of methylmercury.

MERCURY TOXICITY has been known for centuries and was referred to in the works of Hippocrates, Pliny, Dioscorides, and Galen.[50] Jean F. Fernel, known as the "modern Galen," gave the first case report of industrial mercury poisoning in 1557[115]; Freeman described mercury poisoning among hatters in 1860[50]; Hunter and associates[64] reported the neurotoxic effects of organic mercurials a quarter of a century ago.

The first indications of fetal toxicity occurred when frequent abortions were noted in women undergoing mercury treatment for syphilis[3] and when Lomholt detected mercury in stillborn infants of mothers treated with mercury compounds.[97] In recent years sporadic outbreaks of mercury poisoning have occurred throughout the world, with reports of cases involving pregnant mothers and newborn infants. Naturally, questions arise concerning the effects of various mercury compounds during pregnancy and the level of maternal mercury exposure resulting in fetal toxicity. These problems require a consideration of reports of human mercury poisoning during pregnancy, the sources of mercury exposure, maternal uptake and distribution of mercury compounds, placental transport, fetal uptake and distribution, and the effects of mercury compounds on fetal tissues.

Since metallic mercury, mercury salts, and organic mercurials are of interest, the interrelations of these mercury compounds are shown in Fig. 1.

From the Division of Perinatal Biology, Departments of Gynecology and Obstetrics, and Physiology, School of Medicine, Loma Linda University.

This project was supported by United States Public Health Service Grant HD 03807.

Reprint requests: Brian J. Koos, M.D., Boston Hospital for Women, Lying-In Division, Harvard Medical School 221 Longwood Ave., Boston, Massachusetts 02115.

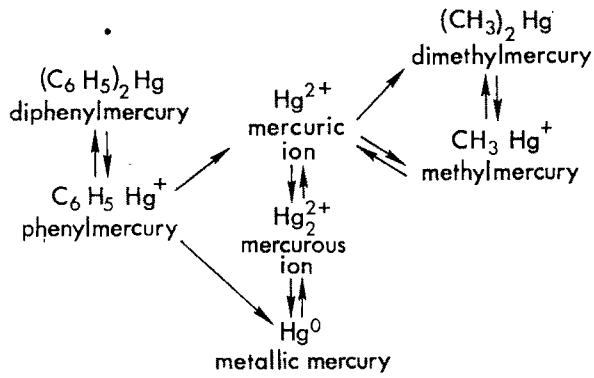


Fig. 1. Various compounds and their interrelations that occur in nature. (Modified from Jernelöv, A.: *In* Miller and Berg: Chemical Fallout, Springfield, Ill., 1969, Charles C Thomas, Publisher.)

Clinical reports of human fetal poisoning by mercury

During the past few years three epidemics and three individual cases of mercury poisoning during pregnancy have been reported. These are summarized in Table I.

1. Minamata, Japan. Near the end of 1953, a strange nervous disorder began afflicting villagers in and around Minamata, a town in Southern Japan.[79, 132] This condition was characterized by a number of neurologic manifestations including mental confusion, convulsions, and coma. About 38 per cent of affected individuals died. Cats, crows, waterfowl, and fish also were affected. Experiments showed that the condition could be produced by feeding fish and shellfish from the bay to mice, rats, and cats.[79] These fish and shellfish contained 9 to 24 μg per gram of methylmercury. Eventually, the source of methylmercury was traced to the effluent discharged into Minamata Bay by a nearby factory.

From 1953 to 1971, 134 cases were reported, including 78 adults and 56 children. During this period 25 infants were born with brain damage.[87, 91, 92, 136] From 1955 to 1959, about 6 per cent of the children born in this area developed cerebral palsy. Other neurologic symptoms included chorea, ataxia, tremors, seizures, and mental retardation.[94] The mothers, all of whom were heavy fish eaters, lacked the typical symptoms, although some experienced mild paresthesias. The fact that these infants had not eaten contaminated fish suggests that the neurologic symptoms resulted from toxicity in utero. On the other hand, the possibility of postnatal acquisition from breast milk cannot be ruled out.[7, 151]

In 1964 an epidemic similar to that in Minamata occurred in Niigata, Japan.[133, 134] As in the Minamata outbreak, the source of methylmercury was traced to the ingestion of fish contaminated by mercury from industrial discharge. Of 46 cases, only one possible prenatal case was reported.

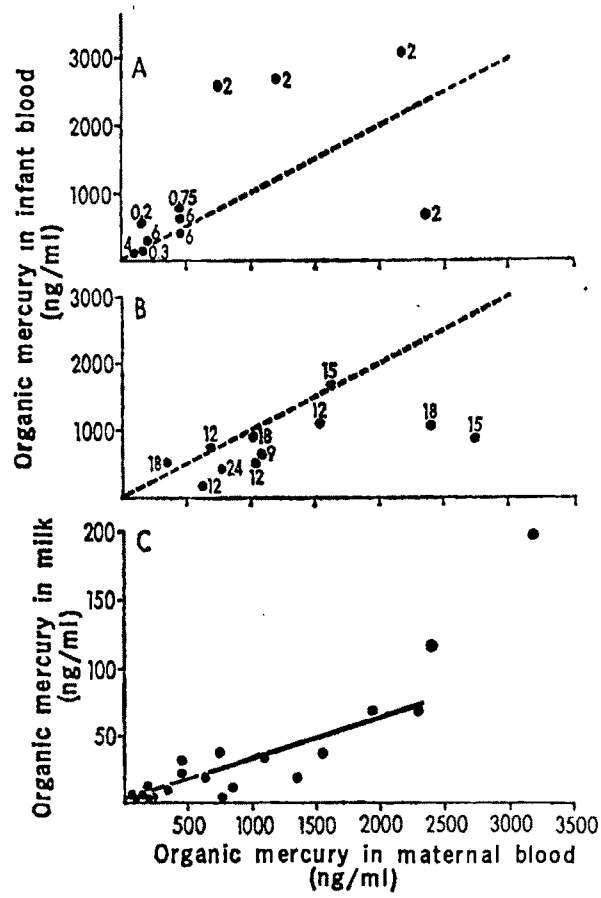


Fig. 2. The concentrations of organic mercury in infant blood and maternal milk as a function of maternal blood concentration. *A*, Blood samples from infants born during and after the epidemic, and thus exposed to methylmercury both in utero and in maternal milk. *B*, Blood samples from infants born prior to the epidemic, and thus only exposed to methylmercury in maternal milk. *C*, Maternal milk samples collected at intervals between April and July, 1972. The number adjacent to the points in *A* and *B* indicate the age of the infant in months at the time of sampling. The dashed line in *A* and *B* are lines of identity. The line in *C* is the linear regression line calculated from the mercury concentrations in maternal blood that were below 2,500 ng. per milliliter. (From Bakir, F., et al.: Science 181: 230, 1973.)

2. Iraq. In September, 1971, barley and wheat grain treated with methylmercury was distributed to Iraqi farmers. The grain was used to make bread containing about 4 mg. of mercury per loaf. A widespread epidemic resulted during 1972.[7] There were 6,530 hospitalized cases with 459 deaths, a mortality rate of 7

Table I. Clinical reports of mercury toxicity in pregnancy

	Year	*Ref. no.*	*Mercurial*	*Cases*
Epidemics:				
Minamata, Japan	1953-1971	86, 92	Methylmercury	25 cases: mental retardation, ataxia, cerebral palsy, tremors, seizures, chorea
U.S.S.R.	1968	8	Ethylmercury	10 cases: mental retardation, decreased birth weight, decreased muscle tone
Iraq	1972	7	Methylmercury	Several cases: severe brain damage
Isolated cases:				
Lund, Sweden	1949	38	Methylmercury	Infant girl: mental retardation, motor disability
King County, Washington	1958	3	Mercuric chloride	Abortion
Alamogordo, New Mexico	1970	122	Methylmercury	Infant boy: seizures

per cent. Symptoms were similar to those of the Minamata epidemic. During this period 31 pregnant women were hospitalized with mercury poisoning. For some undetermined reason the mortality rate of these women in the 20 to 30 year age range was 70 per cent (12 of 17), whereas in women over 30 it was only 16 per cent (two of 12). Blood mercury levels of infants born prior to the epidemic were less than or equal to corresponding maternal values (Fig. 2). This presumably represents poisoning via breast milk, which was shown to contain 5 to 6 per cent of the mercury concentration of maternal blood. In infants born during or after the epidemic mercury blood values were generally greater than maternal values. In these cases the mercury was acquired in utero, during breast feeding, or both. In utero poisoning was particularly suspected in infants less than 2 months old. Several had mercury levels greater than 25 μg per milliliter of blood and demonstrated evidence of severe brain damage.

3. U.S.S.R. In 1968 Bakulina[8] reported 10 cases of prenatal poisoning among mothers who ingested grain treated with ethylmercury. Severe mental retardation was described in three cases and decreased birth weight and muscle tone were noted in others. Since no detailed case histories were given, the extent of postnatal exposure through breast milk is unknown. However, the presence of neurologic symptoms at birth suggests prenatal intoxication.

Outbreaks of poisoning by ingestion of mercury contaminated grain also occurred in Guatemala, Pakistan, and Iraq[59, 100]; however, no fetal or neonatal cases were reported.

4. Lund, Sweden. A pregnant woman and her family, including a young infant, ate mercury-contaminated flour for several months.[38] She had no symptoms of poisoning even though she was excreting mercury up to 0.064 μg per milliliter of urine. She gave birth to an apparently normal, healthy infant girl, without clinical signs of mercury poisoning, whose urine contained less than 0.003 μg per milliliter of mercury. Within a few months, however, the child developed signs of severe mental retardation. While this case does not prove that mercury ingestion during pregnancy causes mental and motor disability, it strongly suggests this effect.

5. King County, Washington. In 1958 a 31-year-old woman developed mercury poisoning complicated by acute renal failure following ingestion of 2.5 Gm. of mercuric chloride in an attempt to induce abortion.[3] Despite gastric lavage and treatment with dimercaprol (BAL) she soon developed complete anuria. Thirteen days after the mercury ingestion, she spontaneously aborted a 5 cm. fetus that appearly grossly normal. The termination of this pregnancy following intake of mercury suggests that mercuric chloride induced the abortion, but it may have resulted from the patient's general illness or therapy.

6. Alamogordo, New Mexico. A 40-year-old woman consumed mercury-contaminated pork during the third to sixth months of pregnancy.[105, 122] Her urine mercury concentrations were 0.47 to 2.91 μg per milliliter and serum levels 2.91 and 0.47 μg per milliliter during the last months of pregnancy. A sample of amniotic fluid analyzed for mercury revealed less than 0.02 μg per milliliter.[35] The mother's symptoms were minimal. She delivered a term male infant who appeared normal, but had some tremulous movements of the extremities which lasted for several days.[118] The neonate's urine mercury level was 2.7 μg per milliliter. An initial electroencephalogram was within normal limits for age, but by 3 months showed widespread abnormal activity. At 6 months of age, the infant developed myotonic jerks and his electroencephalogram was markedly abnormal. Since the infant never nursed from the breast, these symptoms most likely resulted from toxicity acquired in utero.

The cases reported above illustrate that mercury ingestion during pregnancy may affect the fetus and be associated with mental retardation, cerebral palsy, and

seizures in newborn infants. In addition, these lesions developed in the fetus even though the mother had no clinical evidence of mercury poisoning.[87] Maternal exposure occurred through several sources, including contaminated fish, meat from domestic animals fed contaminated grain, direct human ingestion of mercury-treated grain, and ingestion of mercuric salts per se.

Maternal exposure

For centuries mercury exposure has occurred through medical use of mercury compounds. As early as the sixteenth century, calomel was used as a diuretic.[44] From 1493 to 1909 mercury was a widely used treatment for syphilis.[3] Inorganic mercurials also have been used as antiseptic ointments, cathartics, and germicides.[44] In 1834, Philip[103] reported on the value of "minute doses" of mercury in restoring health. He felt that chronic diseases could be treated by frequent ingestion of small doses of mercury and frequently prescribed calomel for indigestion, constipation, and congestive heart failure. He particularly advocated mercury treatment for hepatitis, believing that it could restore liver function. Today mercury therapy is largely limited to less toxic organic compounds, used as topical germicides and diuretics.[44]

Mercury exposure is largely a hazard of certain occupations, such as the production of electrolytic chlorine, electrical apparatus catalysts, thermometers, paints, and amalgamations.[51, 94] Certain professions also may involve mercury exposure. Up to 14 per cent of dental offices had mercury vapor concentrations exceeding 0.1 mg. per cubic meter of air.[55, 74] Doctors' offices may have from 0.004 to 0.006 mg. per cubic meter in rooms where a thermometer has been broken. Even our homes are not exempt, as rooms painted with latex paint can have up to 0.003 mg. per cubic meter concentrations.[43] Exposure to organic mercury compounds can occur in areas of industrial production and usage and in agriculture through seed treatment.

Methylmercury exposure occurs primarily through consumption of contaminated fish. Tuna mercury concentrations average between 0.13 and 0.25 μg per gram, with levels up to 1 μg per gram having been reported.[58] In Sweden the mercury concentration of fish in certain lakes was up to 10 μg per gram.[146] North America has also been affected. In 1935 fish from Lake St. Clair, Canada, had mercury concentrations ranging from 0.07 to 0.11 μg per gram.[73] By 1970 fish from this same lake had concentrations from 0.2 to 7.0 μg per gram. In a California study about 35 to 50 per cent of fish caught in the Sacramento and San Joaquin River area contained mercury levels exceeding 0.5 μg per gram.[37] Fish from Lake Erie may contain up to 1 μg per gram[101]; for comparison fish in the Smoky Mountains contain only 0.002 to 0.059 μg per gram.[62]

Elevated fish concentrations result from mercury contamination of inland and coastal waterways by pollution from natural and industrial sources.[4] Microorganisms in river and lake sediments convert various inorganic and organic mercurials into the most toxic mercury compound, methylmercury.[65, 69, 89, 148] Fish take up methylmercury directly through their gills and indirectly by eating contaminated food.[72] Because methylmercury has an excretion half-time in fish up to several hundred days,[51] it accumulates to concentrations thousands of times greater than in the surrounding water. For instance, perch and pike with mercury levels over 0.1 μg per gram have been found in water containing about 0.0001 μg per gram.[19] An increase in water mercury concentration naturally increases the fish concentrations. Pike downstream from industrial use of mercury slimicides contained up to 20 times greater methylmercury concentrations than similar fish upstream from the pollution point.[19]

Other than fish, most foods ordinarily do not contain mercury in significant concentrations to be a health danger.[135] Flour usually contains less than 3 ng. per gram; milk, less than 1 ng. per gram; eggs, less than 2 ng. per gram; shrimp, 14 ng. per gram.[135] However, game birds may have significant mercury levels, with ducks in North Dakota having up to 2.26 μg per gram in breast meat.[39] Methylmercury-treated seed in Sweden resulted in contamination of many foods. A study in 1966 showed eggs contained 0.029 μg per gram and contained only 0.009 μg per gram in 1967 after methylmercury treatment of seed was prohibited.[146] Porkchops had 0.03 μg per gram in 1966 and only 0.01 μg per gram in 1967.[146]

Maternal absorption, distribution, and excretion

Fetal mercury exposure may follow previous mercury uptake by the pregnant mother. Possible maternal portals of entry include the lungs, gastrointestinal tract, and skin. The degree of maternal mercury uptake depends on several factors, such as the specific chemical form of mercury and the rate of absorption of the compound by the involved route (Table II).

Metallic mercury (Hg^0) is not appreciably absorbed by the gastrointestinal tract under ordinary circumstances. Although oral ingestion of metallic mercury has been considered harmless, it has caused diarrhea and stomatitis.[1] Mercury vapor, being relatively more diffusable, can be readily absorbed by the lungs, with about 80 per cent of inhaled mercury taken up by

Table II. Absorption, placental permeability, and excretion

	Absorption	*Relative placental permeability**	*Excretion*
Metallic mercury	Lungs[14, 83, 143] Skin[97]	10-20[28, 54]	Urine‡ Feces‡ Lungs[84] Breast milk‡
Inorganic salts	Gastrointestinal[97] Lungs† Skin[117]	2[127]	Urine[16] Feces[131] Breast milk[61, 85]
Phenylmercury	Gastrointestinal[97] Lung[97] Skin[97]	1[127]	Urine[131, 17] Feces[131, 17] Breast milk‡
Methylmercury	Gastrointestinal[2] Lung[64, 129] Skin[97]	20[127]	Urine[131] Feces[131] Breast milk[7, 85]

*These are only estimates and are not corrected for relative maternal blood activities.
†Aerosols (Task Group on Lung Dynamics, 1966, Air Quality Criteria for Particulate Matter, 1969).
‡No direct studies, but follows inorganic salt excretion after conversion to Hg^{2+}.

alveoli.[14, 42, 63, 84] Mercury also can be absorbed through the skin, but this is too slow a process to be of much importance except in unusual circumstances.[41]

Unlike metallic mercury, mercuric ions (Hg^{2+}) are more readily absorbed through the gastrointestinal tract (Table II). About 5 to 15 per cent of the total amount ingested is absorbed by this route.[28, 142] Mercurous ions (Hg_2^{2+}) are less water soluble than Hg^{2+} compounds; therefore, they are not as well absorbed orally.[118] Inhaled aerosols of mercuric salts are absorbed by the lungs, although not as well as mercury vapor.[41, 42] Mercuric ions can also be absorbed by the skin, but less so than by other routes.[41]

Organic mercury is absorbed to an even greater extent than the inorganic salts.[41] Two common organic mercurials are methylmercury and phenylmercury. About 80 to 100 per cent of these compounds are absorbed by the gastrointestinal tract, but much of this is subsequently secreted in the bile.[2, 142] Since organic mercurials are volatile and lipid soluble, their vapor readily diffuses through lung alveoli. Skin absorption of these compounds can also occur, particularly through sores or wounds.[37]

In the blood, inorganic mercurials combine with plasma proteins and hemoglobin.[41] Tissues containing the greatest concentrations after acute exposure are kidney, liver, spleen, muscle, and blood.[16, 131] Both mercurous ions and metallic mercury are rapidly converted to mercuric ions by intracellular enzymes.[41] Metallic mercury is more lipid soluble than the mercuric form and diffuses more readily across cell membranes.[84] Because of this, it is more widely distributed than the ionic form and can penetrate into the brain, attaining concentrations 10 times those of mercuric compounds.[13]

Phenylmercury and methylmercury also bind to blood proteins.[10, 41] Phenylmercury is rapidly degraded to inorganic mercury; consequently, after a few days it follows the distribution of mercuric ions.[131] Methylmercury, on the other hand, is a much more stable compound and tends to accumulate in tissues. Being lipid soluble, methylmercury easily diffuses through cell membranes. Because of this, it can attain appreciable concentrations in the brain, approaching 10 to 20 per cent of the total body methylmercury content.[2, 41, 145]

Interestingly, brains of pregnant rats accumulated less methylmecury than those of nonpregnant rats (Fig. 3),[98] suggesting that pregnancy provides some protection against neurologic toxicity caused by methylmercury exposure. In another study, pregnant mice had blood concentrations 40 per cent lower than nonpregnant levels after acute methylmercury exposure.[127] These lower maternal tissue concentrations may reflect a decreased total maternal mercury content resulting from mercury distribution into placental and fetal tissues.[98]

The excretion of inorganic mercury occurs primarily by fecal and urinary routes with a biologic half-life of 30 to 60 days in human subjects.[42] Since phenylmercury is converted to Hg^{2+}, its route of excretion is similar to that of inorganic mercury with probably a similar biologic half-life. Methylmercury is excreted mainly by the fecal route, but some is also excreted in the urine.[2] The biologic half-life is about 70 days in man.[2]

Placental transfer, fetal uptake, and distribution

Mercury compounds, as most other substances, may pass through the placenta into the fetal circulation. Fetal toxicity is a function of how readily these compounds penetrate the placental membranes and of

their degree of accumulation within the fetal central nervous system.

For metallic mercury, up to 0.22 per cent of maternally inhaled mercury vapor (1.9 μg) was present in rat fetal tissues 24 hours after exposure.[28] Of total mercury in the fetal-placental unit the fetus and placenta had approximately equal mercury content.[28, 54] The placenta is even less permeable to inorganic mercury ions. After 24 hours, only 0.01 per cent of an injected dose (0.1 μg) of mercuric chloride was present in rat fetuses.[28] In mice, mercuric chloride (1.5 mg. per kilogram) injected on day 14 of gestation resulted in 0.14 per cent of the injected mercury being transferred to fetal tissues 4 days later.[127] While little mercury entered the fetal circulation, more inorganic mercury was deposited in placental tissues.[16, 127] About 0.52 per cent of injected mercuric chloride (1.9 μg) was found in the rat placenta 24 hours later.[28] It will be noted that the above values are those at a single point in time following maternal administration of a single dose. It would be more valuable to know fetal and maternal values under steady-state conditions, but this data is not available. It is apparent, however, that while placental cells can readily accumulate mercuric ions, relatively small amounts of these compounds enter fetal blood.

Like the inorganic mercurials, little phenylmercury crosses the placenta, with only 0.074 per cent of an injected dose (2.5 mg. per kilogram) being present in mice fetuses 4 days after injection.[127] Placental concentrations were 15 times the fetal values, possibly reflecting placental binding of phenylmercury.[127]

In comparison with the inorganic mercurials and phenylmercury, methylmercury passes more readily through placental tissues. About 1.39 per cent of an injected dose (2.5 mg. per kilogram) crossed the mouse placenta into fetal tissues 4 days after injection on day 14 of gestation, an amount 10 times that for mercuric chloride and almost 20 times the phenylmercury value.[128] In another study, newborn rats contained about 1.16 per cent of the methylmercury given maternal rats at about day 14 of gestation,[86] whereas the maternal rats contained 11 per cent of the original dose at birth.

Reynolds and Pitkin[112] studied methylmercury transfer across the hemochorial placenta in rhesus monkeys. The time course of changes in maternal and fetal blood following maternal injection of a single dose of mercury is shown in Fig. 4, *A*. About 6 hours after exposure, the maternal blood concentrations were 10 times greater than fetal values, suggesting that the placenta may partially protect the fetus from acute mercury exposure.[112] In contrast, a rhesus monkey given methylmercury 6 times over 12 weeks during gestation resulted in fetal blood levels 2.25 times

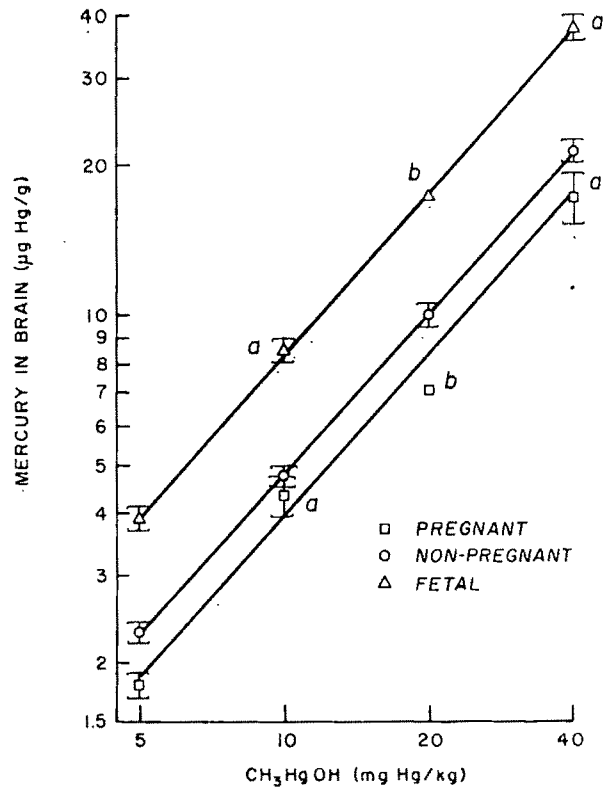


Fig. 3. Mercury concentrations in brains of rats as a function of dose of methylmercury hydroxide given subcutaneously for 7 days. Concentration in the brains of pregnant animals were lower than in nonpregnant controls at any given dose. Mercury concentrations in fetal brains were about twice those of maternal brains. (From Null, D., et al.: Life Sci. 12: 65, 1973.)

greater than maternal concentrations at birth. Therefore, while the placenta may protect the fetus during acute maternal methylmercury exposure, it does not prevent fetal blood mercury accumulation during chronic maternal exposure. The time course of changes following injection of methylmercury into fetal blood are shown in Fig. 4, *B*.

There are several reports of mercury concentrations in human fetal and maternal blood at birth of women with normal exposure to mercury compounds (Table III). It is apparent that the mercury level in blood and tissue is a function of one's place of residence and diet. For instance, normal levels in Japan[128] and Sweden[137] are many times those found in rural Iowa.[101] Studies in both Sweden and Japan have shown that the average mercury concentration of fetal erythrocytes was about 30 per cent greater than maternal values (Fig. 5).[82, 94, 128] In addition, fetal and maternal red cell levels were three to six times greater than corresponding plasma concentrations.[94, 128] Although no differentiation was made as to type of mercury compound, most of the mercury was believed to be methylmercury.[128]

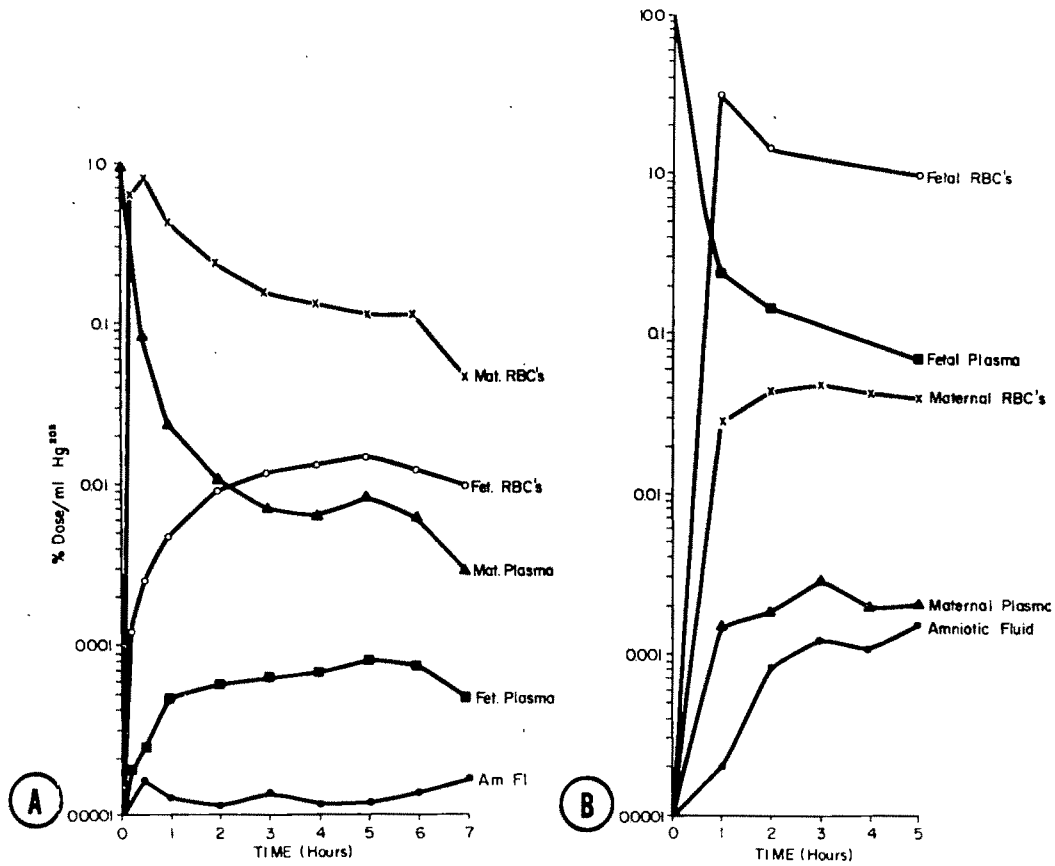


Fig. 4. *A*, Levels of ^{203}Hg in maternal and fetal rhesus monkey circulations following maternal intravenous administration of methylmercury chloride. Values are means of five experiments. *B*, Levels of ^{203}Hg in fetal and maternal blood following fetal intravenous administration of methylmercury chloride. Values are those of a single study. (From Reynolds, W. A., and Pitkin, R. M.: Proc. Soc. Exp. Biol. Med. 148: 523, 1975.)

Table III. Mercury concentrations in normally exposed populations*

Location	*Ref. no.*	*Concentration (μg Hg/Gm.)*			
		Maternal blood	*Placenta*	*Fetal blood*	*Fetal tissue*
Japan	128	0.017†	0.072	0.020†	
Japan	95				Brain 0.16-0.23 Whole body 0.27
Sweden	137	0.006†		0.008†	
Tennessee, U. S. A.	6	0.009	0.021	0.011	
Iowa, U. S. A.	104	0.001	0.002	0.001	

*Table modified from Pitkin et al.: Proc. Soc. Exp. Biol. Med. 151: 565, 1976.

†Values calculated assuming maternal hematocrit = 33 per cent and cord hematocrit = 48 per cent.

Most studies on the distribution of mercury compounds in fetal tissues have been with methylmercury. Fig. 6 indicates that fetal mercury concentration is proportional to the methylmercury content of ingested food under quasi-steady-state conditions.[34] In this study, pregnant mice were given 10 day feedings of tuna containing varying concentrations of methylmercury. A 0.5 μg per gram diet corresponded to a fetal concentration of about 0.5 μg per gram and a 1.0 μg per gram diet resulted in a fetal mercury level of about 1.0 μg per gram. Apparently, doubling the mercury concentration of food doubles the fetal mercury concentration.

Methylmercury accumulates in the fetal nervous system.[85, 88, 98, 150] In pregnant rats given methylmercury on day 15 of gestation, the fetal brain concentration 24 hours later was 67 per cent greater than that of the maternal brain.[85] Fig. 3 shows that fetal rat brain contained about twice the maternal brain concentra

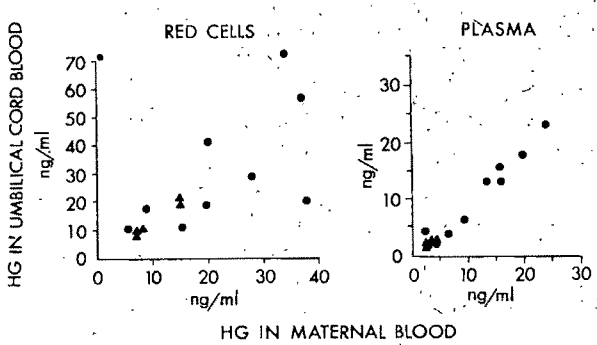


Fig. 5. Mercury concentrations in human fetal erythrocytes and plasma as a function of maternal whole blood mercury concentrations. (Closed circles, data from Suzuki, T., et al.: Bull. Environ. Contam. Toxicol. 5: 502, 1971; triangles data from Tejning, S.: Report 680220, Clin. Occup. Med., Univ. Hosp., Lund, Sweden, 1968.)

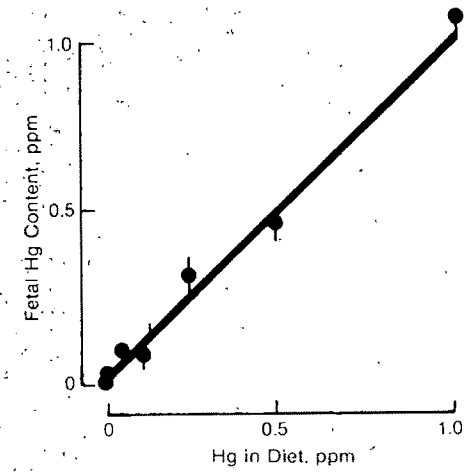


Fig. 6. Net mercury content in μg/g (or ppm) of mice fetuses, as function of mercury content in maternal diet. Values are means ± SEM for 40 animals. (From Childs, E.: Arch. Environ. Health 27: 50, 1973.)

tion 7 days after methylmercury exposure.[98] Another study with rats suggests that these fetal brain levels are not attained rapidly since fetal and maternal brain methylmercury uptakes were identical for the first 2 days following exposure. After this the fetal brain uptake became two to three times the maternal uptake, resulting in the fetal cerebellum having up to four times the maternal cerebellar concentrations and fetal cerebral concentrations being twice the maternal values.[150] These higher fetal brain concentrations may have resulted from the greater fetal blood concentration,[98] from greater fetal brain binding of methylmercury,[151] or from a greater fetal brain half-life.[151]

In man the relative mercury brain concentrations appear to be dose dependent. Table III shows that fetuses of women of average mercury exposure did not have brain concentrations significantly different from those of average adults.[95] This indicates that under ordinary circumstances the fetal brain is not exposed to mercury levels greater than adult values.

Experimental effects in animals

Some details of various studies in experimental animals are outlined in Table IV. Although studies have shown that little mercuric chloride or phenylmercuric acetate enters fetal tissues,[16, 17] embryopathic effects of these compounds have been demonstrated in hamsters.[46] Both of these inorganic compounds appear to result in similar degrees of litter resorption, growth retardation, subcutaneous edema, exencephaly, and anopthalmia. Teratogenic effects, such as cleft lip and palate, rib fusions and syndactylia, were also seen. Phenylmercuric acetate, having spermicidal properties, has been used as a vaginal contraceptive. A study with pregnant mice has shown that 1.1 mg. of phenylmercuric acetate or about one tenth of a contraceptive tablet given per vaginum on day 7 of gestation resulted in fetal growth retardation, tail abnormalities, and embryonic death.[93] The full effects of inorganic mercury and phenylmercury compounds on the fetal nervous system are unknown. What is known, however, is that these compounds can prevent normal fetal growth and development.

Methylmercury compounds can have teratogenic effects in multiple fetal organ systems. In rats,[60, 66] hamsters, and mice[66, 88, 125] various skeletal malformations have been reported, including rib defects, abnormal skeletal calcification, cleft lip and palate, micrognathia, and club feet. Growth retardation, litter resorption, and stillbirth occurred frequently. Methylmercury compounds particularly affected nervous tissue, resulting in cerebellar malformation, nerve degeneration, and hydrocephalus.[60, 88] A study in mice showed that some mothers given methylmercury while pregnant gave birth to neonates having abnormalities while overt poisoning was not detected.[126] These mice had subtle differences from controls in defecation, urination, and swimming patterns. Other changes included a greater period of latency before they started exploring when placed in a test field, and a backing phenomenon in which the mice took at least three steps backward before advancing at the start of exploration.

The frequency of fetal malformations relates to the gestational time of exposure.[92] Mice progeny had the greatest abnormalities when a single methylmercury exposure (30 mg. per kilogram) occurred during days 8 to 12 of gestation. The most vulnerable period was

Table IV. Experimental studies of maternal mercury exposure during gestation on fetuses and neonates

Mercurial	*Species*	*Dosage (mg./Kg.)*	*Gestational days of exposure*	*Route**	*Effects*	*Author*
Mercuric chloride	Rat	—	During gestation	Oral, I.M.	Abortion Neonatal death	3
Mercuric acetate	Hamster	2, 3, 4	8	I.P.	Litter resorption Growth retardation Subcutaneous edema Cleft lip and palate Rib fusion Syndactylia Exencephaly	46
Phenylmercuric acetate	Hamster	5, 7.5, 8, 10	8	I.P.	Same as above	46
Phenylmercuric acetate	Mouse	38	7	Vaginal	Growth retardation Embryonic death Tail abnormalities	92
Methylmercuric chloride	Mouse	0.1	6-17	Oral	No effect	78
	Mouse	1	6-17	Oral	Delayed cerebellar differentiation Decreased cerebellar succinic dehydrogenase, NPND, and cytochrome oxidase	78
	Mouse	5	6-17	Oral	Stillbirths Neonatal death	78
Methylmercuric chloride	Mouse	30	6-13	Oral	Cleft palate Micrognathia Microglossia Generalized edema Brain lesions	66
	Rat	5	0-20	Oral	Crossing phenomenon of hind limb Generalized edema Hydrocephalus Brain defects Death	66
Methylmercuric chloride	Rat	2	9-11	Oral	Nerve degeneration Cerebellar malformation	88
Methylmercuric chloride	Rat	1.3-2	8 doses during 1-20	Oral	Purkinje cell alterations of decreased ribosomes and increased electron density of cytoplasm Granule cell reduction of nucleoli, chromatin, and ribosomes	96
Methylmercuric chloride	Rat	2.5	6-15	Oral	Growth retardation	25
Methylmercuric chloride	Hamster	8	1 dose on 5, 8, or 9	I.P.	Growth retardation Clubfoot Hydrocephalus Litter resorption Death	60
	Hamster	2	1-14	I.P.	Litter resorption Death Fetal malformation Growth retardation	60
Methylmercuric chloride	Rat	5, 10	Preceding and during gestation	—	Stillbirth Intracranial hemorrhage	91
Methylmercuric dicyandiamide	Mouse	2, 4, 8	1 dose during 6-13	I.P.	Growth retardation Developmental retardation Cleft lip and palate Death	125

Table IV—Cont'd

Mercurial	*Species*	*Dosage (mg./Kg.)*	*Gestational days of, exposure*	*Route**	*Effects*	*Author*
Methylmercuric dicyandiamide	Mouse	8	7 or 9	I.P.	Subtle behavioral changes	126
Methylmercuric dicyandiamide	Mouse	4	10	I.P.	Litter resorption	108
Methylmercuric sulfide	Rat	10	Daily doses during gestation	Oral	Growth retardation Neurologic disorder	45
Methylmercuric sulfide or dimethyl sulfide	Cat	5, 10	During gestation	—	Stillbirth Neonatal death	91
Ethylmercuric phosphate	Mouse	40	10	S.C.	Cleft palate Growth retardation	30
Bis-ethylmercury sulfide	Cat	2-3	Daily doses during gestation	Oral	Ataxia Cerebellar hypoplasia	90

*I. M., intramuscular; I. P., intraperitoneal; S. C., subcutaneous.

days 11 and 12 of gestation, at which time all progeny were affected. One hundred per cent had cleft palates, 97 per cent had micrognathia, 77 per cent had microglossia, 21 per cent had generalized edema, 95 per cent had hydrocephalus, and 43 per cent were stillborn.[92] Apparently gestational days 8 to 12 are critical for mouse cephalic development, therefore teratogens given at this time will cause the greatest defects.

One experimental study indicated that an oral dose of 1.0 mg. per kilogram per day of methylmercury was necessary to produce symptoms of poisoning in adult rats[12] whereas, in another study, only 0.1 mg. per kilogram of methylmercury produced symptoms in the rat fetus.[12, 45] Although this suggests that the fetal rat is 10 times more sensitive to methylmercury than adults, this is not necessarily the case as there have not been sufficient animal studies to determine how much more sensitive the fetus actually is.

Cytologic distribution and pathology

The intracellular binding of mercury occurs in molecules rich in sulfhydryl groups (—SH).[140] Such compounds occur in mitochondria, endoplasmic reticulum, the Golgi complex, and nuclear membrane.[98] Neurofiliments and neurotubules are involved to a lesser degree.[32, 152] Methylmercury has also been detected inside the nucleus and nucleolus. A 12- to 15-fold enrichment of mercuric chloride has been reported in the euchromatin of mice given mercuric chloride in drinking water.[23] This mercury accumulation is presumably due to mercury-protein complexes within the euchromatin, although mercury-DNA complexes may also contribute.[23]

In nonpregnant rats, histochemical studies showed methylmercury accumulation in nerve cells, neuroglia, and nerve fibers.[32] In neurons, methylmercury concentrations were greatest in the dorsal root ganglia, whereas neurons of the calcarine cortex, Purkinje cells of the cerebellum, ventral horn motor cells, and cerebellar granule cells showed progressively decreasing concentrations.[32] This was in contrast to the distribution of mercuric chloride in which the decreasing order of mercury concentration was dorsal root ganglia, Purkinje cerebellar cells, ventral horn motor neurons, calcarine cortical neurons, and the granule cells of the cerebellum.[32]

The greatest damage occurs in nervous tissues which accumulate the mercury compound to the greatest extent.[32] Since methylmercury tends to concentrate in both the cerebral cortex and cerebellum, these areas are particularly affected. Degeneration occurs in the cerebral cortical cells and in granule and Purkinje cells of the cerebellum. The rest of the brain is involved to a lesser extent. Degeneration of nerve tracts in the spinal cord can occur as well as in peripheral sensory nerves. In Minamata, human fetal lesions differed from those of the adult in that fetal cerebral cortical involvement appeared more diffuse and fetal brain hypoplasia and malformations frequently occurred while never present in adults.[87] Studies with pregnant rats given methylmercury also produced the same pathologic differences with malformations of the fetal cerebellum more common than degeneration of nerve cells.[88] Histologic changes occurred in the rat cerebral cortex when they were fed a diet containing 0.8 mg. per kilogram of methylmercury, whereas gross distortion

of the cerebellar lobes required 20 mg. per kilogram per day.[88]

Biochemical effects

Mercury compounds affect multiple cellular and subcellular systems. They have a high affinity for proteins, amino acids, purines, pyrimidines, and nucleic acids.[140] Most of the lesions producing toxicity can be explained by the interaction of mercury with these molecules.

By interacting with sulfhydryl groups and disulfide bonds on cell membrane proteins, mercury compounds alter the selective permeability of membranes for ions and nutrients, and possibly block more specific membrane transport processes.[26, 140] An interesting feature of mercury-membrane interaction occurs in mitochondria. Fluorescein mercuric acetate affects the inner mitochondrial membrane, causing both suppression and induction of mitochondrial functions.[124] It suppresses oxidative phosphorylation, calcium transport, and phosphate accumulation, while inducing ATP hydrolysis, K^+ and Mg^{2+} transport, and configurational changes of mitochondria. These are important mechanisms of mercury toxicity since inhibition of mitochondrial function results in cellular death.

Mercury interacts with phosphate and base groups of nucleic acids,[140, 149] changing the intrinsic viscosity and absorption curves of deoxyribonucleic acids (DNA). Methylmercury also denatures animal and bacterial DNA.[56, 140] Organic mercury has caused polyploidy in the root cells of plants[108, 109] and organic mercurials also have been shown to increase XXY nondisjunction in the fruit fly, *Drosophilia melanogaster*.[110] In Sweden, chromosome analysis of human lymphocytes showed increased frequency of chromosome breakage associated with elevated blood mercury concentrations.[120] Both inorganic and organic mercurials can increase the generation time for cell division in *Tetrahymena pyriformis*, a protozoan, an effect possibly caused by interaction of mercury with microtubule proteins.[139] While these studies demonstrate the potential of mercury compounds for genetic alterations, the full implication of these experiments has yet to be determined.

Methylmercury both activated and repressed gene function in asymptomatic rats, affecting DNA, ribonucleic acid (RNA), and protein content of cells.[21, 22] Gene induction occurred in brain and liver cells with increased synthesis of DNA, RNA, and protein. Repression took place in kidney tissue, decreasing these macromolecular concentrations.[21, 22]

Both methylmercury and inorganic mercury increase nerve fiber RNA content in anterior horn motor neurons.[31] This is thought to be a reparative response to damage caused by these mercurials. Both inorganic and organic mercury compounds decrease the RNA content of spinal ganglion neurons, probably as a result of decreased RNA synthesis.[31, 33]

In rats mercuric chloride initially decreased the activity of certain kidney lysosomal enzymes, such as acid phosphohydrolase, β-glucuronidase, and N-acetylglucosaminidase. After several hours, the activity of these same enzymes increased to levels above control values.[141] Mitochondrial cytochrome c-oxidase activity decreased, while microsomal β-glucuronidase activity was increased.[141] Elevated serum glutamic oxalacetic transaminase and lactic dehydrogenase activities have also been reported.[106, 113] Mercury compounds have other effects on body chemistry. Increased plasma galactosidase and plasma catalase activities and decreased erythrocyte cholinesterase activity have been reported in workers exposed to mercury vapor concentrations less than 0.05 mg. per cubic meter.[81] The fact that mercury can alter enzyme activity suggests that this might be one mechanism responsible for fetal and neonatal toxicity.

Diagnosis

The diagnosis of mercury poisoning is based primarily on the history of exposure to mercury compounds with symptoms of intoxication.[5] Acute exposure to mercury vapor can cause coughing, dyspnea, chest pain, cyanosis, excitement, and tremor.[121] In chronic exposure, more subtle symptoms may occur, such as weakness, fatigue, anorexia, weight loss, and gastrointestinal disturbances.[121] Inorganic mercury ingestion causes acute symptoms of thirst, metallic taste, nausea, and abdominal pain. These symptoms are followed by tenesmus, bloody diarrhea, stomatitis, gastritis, colitis, renal tubule degeneration, and death.[1] Chronic ingestion of these compounds results in excessive salivation, loose teeth, and gingivitis.[115] Neurologic signs include nervousness, irritibility, tremors, and slurred speech.[1]

Methylmercury poisoning presents with even more neurologic involvement with mild intoxication; the symptoms include fatigue, headache, and neurasthenia.[64, 118] Paresthesias also can occur in the distal extremities, perioral area, and tongue. With greater exposure, the severity of neurologic involvement increases with intellectual deterioration, spasticity, intention tremor, and paralysis. Cerebellar ataxia, deafness, and constriction of visual fields also can occur.[64, 118] In severe cases, where the concentrations of mercury are more than 2 μg per gram of whole blood, coma and death may result. One problem with methylmercury poisoning is the prolonged period before onset of

symptoms, lasting up to several weeks in some cases.[7, 119]

Urine mercury concentrations are of secondary importance in diagnosis of mercury poisoning. Nonexposed individuals have less than 25 μg per liter.[136] A level of 150 μg per liter or greater is an indication of potentially hazardous exposure.[136] While analysis of mercury in urine is fairly convenient, it should be pointed out that there is a poor correlation between urinary mercury concentrations and mercury exposure.[67, 68] Urine mercury levels may be of some use in inorganic mercury poisoning, but they are useless for estimating methylmercury exposure since large increases of methylmercury blood levels give only slight urine mercury elevations.[83]

Blood mercury levels have been used as an index of inorganic mercury intoxication. The upper limit of unexposed individuals is about 3 μg per 100 ml.[80] While the blood mercury concentration is proportional to the extent of exposure in group studies, individual cases may not show a close correlation.[53] Blood levels of methylmercury correlate to the degree of exposure at steady state,[11] but about 1 year of daily intake is necessary before a steady state is reached.[2] Blood mercury concentrations also may reflect the degree of acute poisoning within a few weeks of exposure.[41]

An important index of exposure is mercury concentration of hair. Since hair concentrations are a function of the total body burden of mercury, they reflect previous exposure levels, and analysis of different lengths of hair indicates the time sequence of exposure.[49, 86, 120] In general, hair concentrations over 150 μg per gram are usually associated with toxicity.[39] The presence of abnormal metabolites such as coproporphyrin also have been suggested as an index of the degree of mercury exposure.[52]

The placenta has been proposed as a readily available tissue that might reflect integrated exposure to environmental minerals over a period of several months.[6] Baglan and associates[6] noted that placental tissue levels of mercury correlated well with both maternal and fetal blood levels. In rats, there is high correlation between the placental content of mercury and the degree of fetal methylmercury exposure,[86] but this is of little value as a diagnostic tool.

For the diagnosis of fetal involvement, it is unlikely that amniocentesis will prove to be of much value. Studies during the methylmercury poisonings in Iraq showed a poor correlation between the degree of maternal exposure and the mercury concentration of amniotic fluid.[7] Of course, there may be a correlation between the amniotic fluid level and the degree of fetal exposure, but this has not been shown.

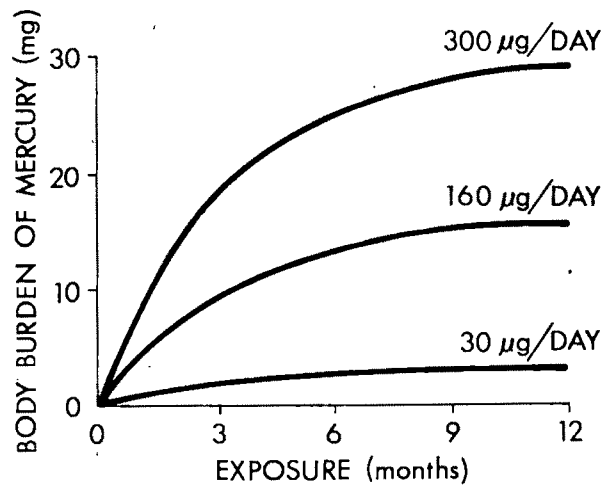


Fig. 7. Theoretical relations between human total body mercury content and the duration of exposure to methylmercury in food. Each curve corresponds to daily intake of a given quantity of mercury. (From Clarkson, W. T.: C. R. C. Crit. Rev. Toxicol. 2: 203, 1972.)

Treatment

In treating a pregnant woman exposed to mercury, one should remember the toxicity of these compounds; appropriate treatment should be started as soon as possible. The first step, obviously, is to prevent immediately any further exposure. Supportive care should be given when necessary to maintain vital functions. More definitive treatment is based on the type and degree of exposure.

For acute inorganic mercury ingestion, treatment includes swallowing egg white or milk to help minimize absorption of mercuric ions.[5] A 5 per cent sodium formaldehyde sulfoxylate solution taken orally decreased mercury absorption by reducing mercuric ions to the metallic form, which is not absorbed.[5] Systemic therapy includes the use of dimercaprol (BAL), calcium disodium edetate, and N-acetyl-D,L-penicillamine, compounds which help eliminate mercury from body tissues.[5]

BAL is useful only for severe poisoning, since it causes frequent local and systemic side effects.[20] This compound combines with mercury, and the BAL-mercury complexes are excreted in the urine.[27] BAL should not be used in cases of chronic poisoning since it increases mercury uptake by brain tissue.[15] Penicillamine also combines reversibly with mercury and takes up mercury from protein-mercury complexes. Penicillamine can produce toxic side effects resulting from inhibition of pyridoxine-dependent metabolic pathways.[20, 147] In experimental studies, spironolactone increased the biliary secretion of inorganic mercury.[57, 114] The use of these compounds in pregnant women is

probably warranted, even though the compounds themselves are potentially harmful to the fetus.

Treatment for methylmercury poisoning has been largely symptomatic. Chelating agents, such as BAL and calcium disodium edetate, are of limited value due to the relatively slight degree of dissociation of methylmercury into inorganic mercury ions. In rats, penicillamine reduced fetal brain methylmercury concentrations and prevented morphologic brain changes.[88] During the outbreak of mercury poisoning in Iraq, N-acetyl-D,L-penicillamine was tried with mixed successs.[7] In some individuals it appeared to increase methylmercury excretion but in others little effect was seen.[7, 76] There have been no reports regarding the effectiveness of penicillamine in reducing human fetal damage due to methylmercury poisoning.

Pyridoxine-5-thiol has been shown to reduce methylmercury concentrations of brain and liver of poisoned rats.[130] Recent studies have shown that thiol resins effectively increase methylmercury excretion.[7, 29, 130] Polythiol resin given in a 1 per cent concentration with food doubled the rate of methylmercury excretion in mice.[29] Normally about 10 per cent of ingested methylmercury is excreted into the bile, with only 3 per cent excreted in the feces, indicating that a large amount is reabsorbed. The polythiol resin combines with methylmercury in the intestinal tract, preventing reabsorbtion.[29] By increasing the fecal excretion of methylmercury, the blood level is lowered, shifting the net movement of methylmercury from the tissues to the blood. Polythiol resin seems ideally suited for the treatment of pregnant women, as it is not absorbed, and a new chemical with unknown fetal effects is not introduced into the mother's circulatory system.

Evaluating the risk

No studies have clearly outlined the mercury exposure for pregnant women. However, some pharmacologic principles have been used to estimate the level of reasonably safe exposure. These principles relate to the amount ingested, the duration of exposure, excretory rate, and sensitivity. A certain mercury dose given acutely may produce toxic effects, whereas the same total dose distributed over a period of time may give no evidence of mercury poisoning. Of course, this is because some excretion occurs over the period of chronic exposure, resulting in lower concentrations in various tissues. On the other hand, a dose of mercury given acutely may not produce symptoms, whereas the same dose given repeatedly over an extended period of time may eventually cause poisoning. In this case, excretion fails to keep pace with intake, resulting in accumulation to toxic levels. Such accumulation does not go on indefinitely, as eventually a steady state is reached in which excretion equals intake. For methylmercury the equilibrium body content is about 100 times the daily intake (Fig. 7).[2] How rapidly this steady state is attained depends largely on the rate of mercury excretion. In Iraq, methylmercury elimination varied greatly. While the mean half-time was 65 days, the range was from 40 to 105 days.[7] Another consideration is the individual sensitivity to mercury compounds. There is great individual variation in the total degree of exposure required to produce symptoms of poisoning. For example, during the methylmercury poisonings in Iraq in 1972, the estimated body burden of mercury necessary to produce paresthesia in adults varied from 25 to 200 mg.[7] Some Swedish people had blood mercury concentrations three times the level associated with death in Minamata, Japan.[19, 116] As previously stated, the fetus appears more sensitive than adults to methylmercury.[87] Exposure guidelines should take into account individual variations of metabolism and response to mercury compounds.

Mercury toxicity also depends on its chemical form (Table V). Acute experiments in mice have shown the intraperitoneal LD_{50} to vary from 5 mg. of mercury per kilogram for mercuric chloride to 8 mg. of mercury per kilogram for phenylmercury and 14 mg. of mercury per kilogram for methylmercury.[129] Thus, inorganic mercury appears to be the most toxic form following acute exposure. On the other hand, chronic oral mercury intake resulting in minimal toxic effects in man has been estimated to be 28 mg. of mercury per day for inorganic salts (Hg^{2+}), 0.75 mg. of mercury per day for phenylmercury, and 0.3 mg. of mercury per day for methylmercury.[42] Part of the lower toxicity of inorganic mercury results from its decreased gastrointestinal absorption. For the fetus, there are insufficient data to establish which mercurial is the most toxic during acute exposure. However, for chronic exposure, the most toxic is methylmercury since it more readily penetrates placental membranes and accumulates in fetal tissues. Metallic mercury may be the next most toxic, with the least toxic probably being phenylmercury and inorganic mercury compounds.[41]

Guidelines for mercury exposure also should allow for subclinical effects. Mercury can cause cellular, subcellular, or biochemical alterations at levels not sufficient to produce overt poisoning. As previously noted, rat progeny whose mothers were exposed to methylmercury during pregnancy underwent subtle behavioral changes.[126] Neuroanatomic alterations can occur without clinical evidence of neurologic impairment. For instance in rats a dose of 1 mg. per kilogram per day of methylmercury produced both morphologic

Table V. Relative toxicity of mercury compounds

	Acute (mg. Hg/Kg.)*	*Chronic† (mg. Hg/Kg./day)*
Mercuric salt	5	28
Phenylmercury	8	0.75
Methylmercury	14	0.3

*Intraperitoneal LD_{50} in mice.[129]

†Minimum oral toxicity in human subjects.[42]

Table VI. Toxic mercury concentrations in human subjects

	Concentration (μg Hg/Gm.)
Adult:	
Blood	0.2[12]*
Brain	5[12]*
Total body content	
Paresthesia	25 mg.[7]†
Death	200 mg.[7]†
Fetus and infant:	
Blood	<3[7]
Brain	
2.5 yr. of age	0.3[87]‡
6.3 yr. of age	0.7[87]‡

*Estimated minimum toxic concentration.

†Threshold levels.

‡Brain concentration at autopsy, and does not necessarily reflect neonatal concentration.

and neurologic changes, whereas 0.5 mg. per kilogram per day exposure produced the morphologic changes in the absence of overt neurologic deficits (C. A. Grant, quoted by Skerfving[119]). Thus, overt toxicity is not a sensitive enough indicator of mercury toxicity.

Maximum exposure limits for toxic compounds usually incorporate a safety factor of at least 10 when the minimum toxic levels are calculated from human data and at least 100 when they are calculated from animal data.[27] This safety factor protects against individual variations of excretory rates, sensitivity, and subclinical effects. Table VI lists some of the minimum tissue concentrations associated with adult toxicity and some values associated with fetal toxicity.

The maximum allowable mercury concentrations in air have been established: 0.05 mg. per cubic meter for mercury vapor, 0.10 mg. per cubic meter for inorganic mercury salts and phenylmercury compounds, and 0.01 mg. per cubic meter for methylmercury (Table VII).[41] The value for mercury vapor may not be low enough, as central and autonomic nervous system excitability has been reported among workers in Russia exposed to 0.01 to 0.03 per cubic meter.[41, 42] In view of the potential for fetal harm, it has been recommended that pregnant women should not work in areas where

Table VII. Maximum allowable concentrations*

Mercury vapor	0.05 mg./$M.^3$ of air
Inorganic mercury salts	0.10 mg./$M.^3$ of air
Phenylmercury	0.10 mg./$M.^3$ of air
Methylmercury	0.01 mg./100 ml. of blood

*These values derived from recommendations of an international committee in 1969. (Friberg, L. T.: Arch. Environ. Health, 19: 891, 1969.)

Table VIII. Exposure limits for women of childbearing age

	Previous guidelines	*Present recommendations*
Occupational:		
Mercury vapor	Should not be exposed to "elevated" levels[116]	<0.01 mg./$M.^3$ of air
Aerosols, of inorganic mercury salts	Should not be exposed to "elevated" levels[116]	<0.02 mg./$M.^3$ of air
Phenylmercury	Should not be exposed to "elevated" levels[116]	<0.02 mg./$M.^3$ of air
Methylmercury	None[41]	None
Fish:		
Fish concentration	<0.25 μg of Hg/Gm.[75]	—
Total methylmercury ingestion	<0.025 μg of Hg/day[12] (for 60 Kg. woman)	—
Quantity of fish	—	<350 Gm./wk.*

*This value is based on a total methylmercury consumption of 0.025 μg per day and a fish concentration of 0.5 μg of Hg per gram.

elevated air levels of mercury compounds may be anticipated (Table VIII).[116]

The maximum allowable blood concentration for those exposed to methylmercury has been calculated from the Minamata experience. Since no evidence of mercury poisoning was found in those with less than 0.2 μg of mercury per milliliter, an expert committee has recommended that the maximum allowable concentration of mercury should be 0.1 μg per milliliter of whole blood.[41] Exposure to 0.01 mg. per cubic meter in air for 8 hours a day probably would not exceed this blood value.[41]

Swedish workers have developed the concept of "acceptable daily intake," that is, the amount of daily methylmercury taken over a long time which will not endanger the individual to mercury poisoning.[42] Using an excretion rate of 1 per cent per day, they calculated that a daily intake of 0.3 mg. per day for a 70 kilogram person would give a blood value of 0.2 μg per milliliter, corresponding to the lowest blood levels known to

cause toxicity.[42] Including a safety factor of 10, the acceptable daily intake of methylmercury was set at 0.03 mg. per day for a 70 kilogram person, corresponding to 0.025 mg. per day for a 60 kilogram woman (Table VIII).[42]

The Federal Food and Drug Administration has set an interim guideline of 0.5 μg per gram of methylmercury for fish; fish with higher concentrations cannot be sold.[40a, 119] Sweden has adopted a more liberal limit of 1 μg per gram.[119]

There have been no official recommendations for pregnant women regarding methylmercury exposure. However, it has been suggested that pregnant women should not regularly consume fish with over 0.25 μg per gram concentration of methylmercury (Table VIII).[75] It has also been recommended that women of childbearing age should not work in areas at risk to methylmercury (alkyl) exposure.[41]

The toxic levels of methylmercury in fish cannot be directly applied to other foods. For example, quail given a 20 μg per gram diet of methylmercury containing 17 per cent tuna survived longer than those given the same quantity of methylmercury in a grain diet.[47] This may be because fish contain relatively high concentrations of selenium (Se), a trace metal which may decrease mercury toxicity by competitive binding to sulfhydryl groups[47, 102] or by forming Se-Hg complexes.[78] Selenium also may help protect the fetus against inorganic mercury. In rats, selenium increased the maternal blood levels and prolonged maternal retention of mercuric ion while it decreased the amount of mercuric ion which entered fetal tissues.[101] Selenium is an example of a heavy metal contaminant that may actually be beneficial. The converse may also be true since there may be chemicals, metals, or drugs which increase mercury toxicity.

Recommendations

Table VIII lists the mercury exposure limits we recommend for women of childbearing age. For mercury vapor, the maximum allowable concentration of 0.05 mg. per cubic meter may not provide sufficient protection for the fetus since nervous excitability and enzyme concentration changes have been noted in adults exposed to 0.01 to 0.05 mg. per cubic meter.[42, 81] Because of this, women of childbearing age should not be exposed to mercury vapor concentrations greater than 0.01 mg. per cubic meter. Likewise, the maximum allowable inorganic aerosols and phenylmercury compounds should be lowered from 0.10 to 0.02 mg. per cubic meter. Women of childbearing age should not be exposed to any occupational risk of methylmercury (alkyl) exposure.

While the "acceptable daily intake" of 0.025 mg. of methylmercury may protect the mother, it may not protect the fetus against subclinical toxicity.[30] How much more sensitive the human fetus is than the mother is not known, and there are insufficient animal data to be able to extrapolate to human beings. In addition, the neurologic examination was the only means used to diagnose mercury toxicity[12]; consequently, subclinical toxicity in adults might have occurred at blood concentration below the 0.2 μg of mercury per gram level used to calculate the "acceptable daily intake" value.

Past guidelines for calculating the maximum allowed fish consumption required knowing both the tissue concentration of mercury and the weight of the fish. A more convenient method would require knowing only the weight of the fish, while assuming it has the maximum allowable concentration (0.5 μg per gram). According to this method, the 0.025 mg. of mercury per day limit would correspond to a daily intake of 50 Gm. of fish containing 0.5 μg of mercury per gram or about 350 Gm. per week. Since the maximum allowed fish concentration of 0.5 μg of mercury per gram is about twice the average tuna value,[58] an additional margin of safety for the fetus is provided.

It should be emphasized that the 350 Gm. per week limit represents a level of reasonably safe exposure and does not represent a maximum no-effect value for the fetus. Moreover, this value is for weekly fish ingestion over an indefinite period of time; therefore, greater amounts might be eaten some weeks when lesser amounts are eaten other weeks. Finally, the average fish consumption in the United States is 120 Gm. per week,[94] indicating that the average woman's intake is well below the 350 Gm. per week value.

The above recommendations are for women who have one major source of mercury exposure. It is possible that some women may be exposed to mercury both at work and at home, resulting in additive exposure above the suggested limits. In some cases the methylmercury content of some foods other than fish might be great enough to become a significant source of exposure, and fish consumption should be reduced accordingly. In addition, fish caught for personal consumption may contain greater concentrations than the FDA limit[37]; therefore, pregnant women of families who catch and eat large amounts of fish from mercury-contaminated waters should be warned of this danger.

These recommended limits for mercury exposure are to be regarded as tentative and should be adjusted according to the results of further studies.

Additional animal experiments in a variety of species

need to be undertaken to establish thresholds of overt and subtle toxicity for different gestational ages. These studies should be done in both steady-state and pulse-exposure preparations. Studies should be initiated to determine the possible inhibition or activation of enzymes in the fetus and placenta and to determine possible changes in placental permeability caused by mercury binding to placental membranes. Methylmercury appears to have a greater affinity for fetal hemoglobin than maternal hemoglobin, a phenomenon as yet unexplained. There is a need for further work to determine if methylmercury compounds can cause genetic changes in sperm, ova, or the developing embryo. A method of estimating the degree of fetal mercury exposure in exposed pregnant women should be devised with criteria established for abortion. Retrospective and prospective studies should be done on pregnant women exposed to mercury compounds to study the difference from controls of abortions, stillbirths, congenital defects, cerebral palsy, mental retardation, enzyme alterations, and the more subtle effects such as behavioral disorders. Most importantly, these studies should correlate so that better estimates of maternal mercury exposure which do not endanger the human fetus can be determined.

Conclusions

All mercury compounds can cause fetal harm, but methylmercury has the greatest toxicity. Occupational exposure to mercury compounds and heavy consumption of contaminated fish appear to be the major sources of exposure for the pregnant woman. Metallic mercury crosses the placenta whereas the inorganic mercuric compounds are less able to do so. Methylmercury compounds more readily cross the placenta and accumulate in fetal tissues. Inorganic mercuric and methylmercuric compounds have been shown to have embryopathic and teratogenetic effects in animals; several cases of human fetal poisoning also have been reported. The diagnosis of mercury poisoning in pregnant women is primarily based on history, symptoms, and signs, whereas mercury levels of maternal blood and urine are of less diagnostic importance. Treatments of inorganic and methylmercury poisoning differ, with specific therapy for inorganic mercury poisoning including BAL, penicillamine, and calcium disodium edetate. Methylmercury poisoning therapy has been largely symptomatic, although penicillamine and polythiol resins show promise. Suggested guidelines for mercury exposure include 0.01 and 0.02 mg. per cubic meter for mercury vapor and for inorganic and phenylmercuric aerosols respectively. Pregnant women should not be exposed to methylmercury compounds and should not eat more than 350 Gm. of fish per week. Finally, additional studies are needed to evaluate further the fetal risk to varying maternal blood levels of mercury in order to determine more accurately the safe limits of mercury exposure for women of childbearing age.

REFERENCES

1. Aaronson, R., and Spiro, H.: Mercury and the gut, Dig. Dis. **18:** 583, 1973.
2. Aberg, B., Ekman, L., Falk, R., Greitz, U., Persson, G., and Snihs, J.: Metabolism of methyl mercury (^{203}Hg) compounds in man. Excretion and distribution, Arch. Environ. Health **19:** 478, 1969.
3. Afonso, J., and De Alvarez, R.: Effects of mercury on human gestation, Am. J. Obstet. Gynecol. **80:** 145, 1960.
4. Anonymous: Extent of mercury pollution much wider than once seen, Hosp. Trib. June 28, 21, 1971.
5. Arena, J. M.: Treatment of mercury poisoning, Mod. Treat. **8:** 619, 1971.
6. Baglan, R. J., Brill, A. B., Schulert, A., Wilson, D., Larsen, K., Dyer, N., Mansour, M., Schaffner, W., Hoffman, L., and Davies, J.: Utility of placental tissue as an indicator of trace element exposure to adult and fetus, Environ. Res. **8:** 64, 1974.
7. Bakir, F., Damluji, S., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al-Rawi, N., Tikriti, S., Dhahir, H., Clarkson, T., Smith, J., and Doherty, R.: Methylmercury poisoning in Iraq. An interuniversity report, Science **181:** 230, 1973.
8. Bakulina, A. V.: [The effect of a subacute ethylmercury coated grain poisoning on the progeny], Soviet Med. **31:** 60, 1968.
9. Baltrukiewicz, A.: Accumulation of mercury in genital organs and fetuses at different periods of pregnancy after intravenous administration of ^{203}Hg-Neohydrin, Acta Physiol. Pol. **21:** 645, 1970.
10. Barltrop, D., and Smith, A.: Mercury binding to human haemoglobin, Experientia **29:** 1178, 1973.
11. Berglund, F., and Berlin, M.: Risk of methylmercury cumulation in man and mammals and the relation between body burden of methylmercury and toxic effects, *in* Miller, M. W., and Berg, G. G., editor: Chemical Fallout. Current Research on Persistent Pesticides, Springfield, Ill., 1969, Charles C Thomas, Publisher, pp. 258-269.
12. Berglund, F., Berlin, M., Birke, G., Von Euler, U., Friberg, L., Holmstedt, B., Jonsson, E., Ramel, C., Skerfving, S., Swensson, Å., and Tejning, S.: Methylmercury in fish. A toxicologic-epidemiologic evaluation of risks. Report of an expert group, Nord. Hyg. Tidsskr. Suppl. 4: 1-364, 1971.
13. Berlin, M., Fazackerley, J., and Nordberg, G.: The uptake of mercury in the brain of mammals exposed to mercury vapor and to mercuric salts, Arch. Environ. Health **18:** 719, 1969.
14. Berlin, M., Nordberg, G., and Serenius, F.: On the site and mechanism of mercury vapor resorption in the lung. A study in the guinea pig using mercuric nitrate Hg^{203}, Arch. Environ. Health **18:** 42, 1969.

15. Berlin, M., and Ullberg, S.: Increased uptake of mercury in mouse brain caused by 2,3-dimercaptopropanol, Nature **197:** 84, 1963.
16. Berlin, M., and Ullberg, S.: Accumulation and retention of mercury in the mouse. I. An autoradiographic study after a single intravenous injection of mercuric chloride, Arch. Environ. Health **6:** 589, 1963.
17. Berlin, M., and Ullberg, S.: Accumulation and retention of mercury in the mouse. II. An autoradiographic comparison of phenylmercuric acetate with inorganic mercury, Arch. Environ. Health **6:** 602, 1963.
18. Berlin, M., and Ullberg, S.: Accumulation and retention of mercury in the mouse. III. An autoradiographic comparison of methylmercuric dicyandiamide with inorganic mercury, Arch. Environ. Health **6:** 610, 1963.
19. Birke, G., Johnels, A., Plantin, L., Syostrand, B., Skerfving, S., and Westermark, T.: Studies on humans exposed to methyl mercury through fish consumption, Arch. Environ. Health **25:** 77, 1972.
20. Brown, J., and Kulkarni, M.: Review of the toxicity and metabolism of mercury and its compounds, Med. Services J. **23:** 786, 1967.
21. Brubaker, P., Herman, S., Lucier, G., Alexander, L., and Long, M.: DNA, RNA, and protein synthesis in brain, liver and kidneys of asymptomatic methylmercury treated rats, Exp. Molec. Pathol. **18:** 263, 1973.
22. Brubaker, P., Lucier, G., and Klein, R.: The effects of methylmercury on protein synthesis in rat liver, Biochem. Biophys. Res. Commun. **44:** 1552, 1971.
23. Bryan, S. E., Lambert, C., Hardy, K. J., and Simons, S.: Intranuclear localization of mercury in vivo, Science **186:** 832, 1974.
24. Cassano, G., Viola, P., Ghetti, B., and Amaducci, L.: The distribution of inhaled mercury (Hg^{203}) vapors in the brain of rats and mice, J. Neuropathol. Exp. Neurol. **28:** 308, 1969.
25. Casterline, J., Jr., and Williams, C. H.: Elimination pattern of methyl mercury from blood and brain of rats (dams and offspring) after delivery, following oval administration of its chloride salt during gestation, Bull. Environ. Contam. Toxicol. **7:** 292, 1972.
26. Clarkson, T. W.: The pharmacology of mercury compounds, Ann. Rev. Pharmacol. **12:** 375, 1972.
27. Clarkson, T. W.: Recent advances in the toxicology of mercury with emphasis on alkylmercurials. CRC—Crit. Rev. Toxicol. **2:** 203, 1972.
28. Clarkson, T., Magos, L., and Greenwood, M.: The transport of elemental mercury into fetal tissues, Biol. Neonate **21:** 239, 1972.
29. Clarkson, T., Small, H., and Norseth, T.: Excretion and absorption of methyl mercury after polythiol resin treatment, Arch. Environ. Health **26:** 173, 1973.
30. Clegg, D. J.: Embryotoxicity of mercury compounds, *in* Special Symposium on Mercury in Man's Environment, Proc. R. Soc. Can., Ottawa, Canada, 1971, pp. 141-148.
31. Chang, L., Desnoyers, P., and Hartmann, H.: Quantative cytochemical studies of RNA in experimental mercury poisoning. I. Changes in RNA content, J. Neuropathol. Exp. Neurol. **31:** 489, 1972.
32. Chang, L., and Hartmann, H.: Electron microscopic histochemical study on the localization and distribution of mercury in the nervous system after mercury intoxication, Exp. Neurol. **35:** 122, 1972.
33. Chang, L., Martin, A., and Hartmann, H.: Quantitative autoradiographic study of the RNA synthesis in the neurons after mercury intoxication, Exp. Neurol. **37:** 62, 1972.
34. Childs, E.: Kinetics of transplacental movement of mercury fed in a tuna matrix to mice, Arch. Environ. Health **27:** 50, 1973.
35. Curley, A., Sedlak, V., Girling, E., Hawk, R., Barthel, W., Pierce, P., and Likosky, W.: Organic mercury identified as the cause of poisonings in humans and hogs, Science **172:** 65, 1971.
36. Dales, L. D.: The neurotoxicity of alkyl mercury compounds, Am. J. Med. **53:** 219, 1972.
37. Dales, L., Kahn, E., and Wei, E.: Methylmercury poisoning. An assessment of the sportfish hazard in California, Calif. Med. **114:** 13, 1971.
38. Engleson, G., and Herner, T.: Alkyl mercury poisoning, Acta Paediatr. Scand. **41:** 289, 1952.
39. Eyl, T. B.: Alkylmercury contamination of foods, J. A. M. A. **215:** 287, 1971.
40. Felton, J., Kahn, E., Salick, B., Van Natta, F., and Whitehouse, M.: Heavy metal poisoning: Mercury and lead, Ann. Intern. Med. **76:** 779, 1972.

40a. Fed. Reg. **39:** 42738, 1974.

41. Friberg, L. T. (Chairman), Expert Committee: Maximum allowable concentrations of mercury compounds. Report of an international committee, Arch. Environ. Health **19:** 891, 1969.
42. Friberg, L., and Vostal, J., editors: Mercury in the environment. A toxicological and epidemiological appraisal. PB-205 000, National Technical Information Service, U. S. Department of Comnerce, U. S. Govt., 1971.
43. Foote, R. S.: Mercury vapor concentrations inside buildings, Science **177:** 513, 1972.
44. Friedman, H. L.: Relationship between chemical structure and biological activity in mercurial conpounds, Ann. N. Y. Acad. Sci. **65:** 461, 1957.
45. Fujita, E.: Experimental studies on organic mercury poisoning on the behavior of Minamata disease causal agent in the maternal bodies and its transference to their infants via either placenta or breast milk, J. Kumamoto Med. Soc. **43:** 47, 1969.
46. Gale, T., and Ferm, V.: Embryopathic effects of mercuric salts, Life Sci. **10:** 1341, 1971.
47. Ganther, H. E., Goudie, C., Sunde, M. L., Kopecky, M. J., Wagner, P. P., Oh, S., and Hoekstra, W.: Selenium: Relation to decreased toxicity of methylmercury added to diets containing tuna, Science **175:** 1122, 1972.
48. Garrett, N., Garrett, R., and Archdeacon, J.: Placental transmission of mercury to the fetal rat, Toxic Appl. Pharmacol. **22:** 649, 1972.
49. Giovanoli-Jakubczak, T., and Berg, G. G.: Measurement of mercury in human hair, Arch. Environ. Health **28:** 139, 1974.
50. Goldwater, L. J.: From Hippocrates to Ramazzini: Early history of industrial medicine, Ann. Med. Hist. **8:** 27, 1936.
51. Goldwater, L., and Clarkson, T.: Mercury, *in* Lee, D. H. K., editor: Metallic contaminants and human health, New York, 1972, Academic Press, Inc., pp. 17-55.
52. Goldwater, L. J., and Joselow, M. M.: Absorption and excretion of mercury in man. XII. Effects of mercury exposure on urinary excretion of coproporphyrin and delta-aminolevulinic acid, Arch. Environ. Health **15:** 327, 1967.
53. Goldwater, L., Ladd, A., and Jacobs, M.: Absorption and excretion of mercury in man. VII. Significance of mercury in blood, Arch. Environ. Health **9:** 735, 1964.
54. Greenwood, M., Clarkson, T., and Magos, L.: Transfer of metallic mercury into the foetus, Experientia **28:** 1455, 1972.
55. Gronka, P., Bobkoskie, R., and Tomschick, G.: Mercury vapor exposures in dental offices, J. Am. Dent. Assoc. **81:** 923, 1970.
56. Gruenwedel, D., and Davidson, N.: Complexing and denaturation of DNA by methylmercuric hydroxide. I. Spectrophotometric studies, J. Molec. Biol. **21:** 129, 1966.

57. Haddow, J., Fish, C., Marshall, C., and Lester, R.: Biliary excretion of mercury enhanced by spironolactone, Gastroenterology **63:** 1053, 1972.
58. Hammond, A.: Mercury in the environment: natural and human factors, Science **171:** 788, 1971.
59. Haq, I. U.: Agrosan poisoning in man, Br. Med. J. **1:** 1579, 1963.
60. Harris, S., Wilson, J., and Printz, R.: Embryotoxicity of methyl mercuric chloride in golden hamsters, Teratology **6:** 139, 1973.
61. Howe, M., McGee, J., and Lengemann, F.: Transfer of inorganic mercury to milk of goats, Nature **237:** 516, 1972.
62. Huckabee, J. W., Feldman, C., and Talmi, Y.: Mercury concentrations in fish from the Great Smoky Mountains National Park, Anal. Chim. Acta **70:** 41, 1974.
63. Hughes, W. L.: A physichochemical rationale for the biological activity of mercury and its compounds, Ann. N. Y. Acad. Sci. **65:** 454, 1957.
64. Hunter, D., Bomford, R., and Russell, D.: Poisoning by methyl mercury compounds, Q. J. Med. **35:** 193, 1940.
65. Imura, N., Sukegawa, E., Pan, S., Nagao, K., Kim, J., Kim, T., Kwan, T., and Ukita, T.: Chemical methylation of inorganic mercury with methylcobalamin, a vitamin B_{12} analog, Science **172:** 1248, 1971.
66. Inouye, M., Hoshino, K., and Murakami, U.: Effect of methylmercuric chloride on embryonic and fetal development in rats and mice, Ann. Rep. Res. Inst. Environ. Med. Nagoya Univ. **19:** 69, 1972.
67. Jacobs, M., Ladd, A., and Goldwater, L.: Absorption and excretion of mercury in man. III. Blood mercury in relation to duration of exposure, Arch. Environ. Health **6:** 634, 1963.
68. Jalili, M. A., and Abbasi, A. H.: Poisoning by ethyl mercury toluene sulphonanilide, Br. J. Industr. Med. **18:** 303, 1961.
69. Jensen, S., and Jernelöv, A.: Biological methylation of mercury in aquatic organisms, Nature **223:** 753, 1969.
70. Jernelöv, A.: Conversion of mercury compounds, *in* Miller, M., and Berg, G., Chemical Fallout. Current Research on Persistent Pesticides, Springfield, Ill., 1969, Charles C Thomas, pp. 68-74.
71. Joensuu, O. I.: Fossil fuels as a source of mercury pollution, Science **172:** 1027, 1971.
72. Johnels, A., and Westermark, T.: Mercury contamination of the environment in Sweden, *in* Miller, M. W., and Berg, G. G., editors: Chemical Fallout. Current Research on Persistent Pesticides, Springfield, Ill., 1969, Charles C Thomas, Publisher, pp. 221-239.
73. Joselow, M., Louria, D., and Browder, A.: Mercurialism: Environmental and occupational aspects, Ann. Intern. Med. **76:** 119, 1972.
74. Joselow, M. M., Ruiz, R., and Goldwater, L. J.: Absorption and excretion of mercury in man. XV. Occupational exposure among dentists, Arch. Environ. Health **17:** 39, 1968.
75. Kahn, E.: Perspective on tuna fish, N. Engl. J. Med. **285:** 49, 1971.
76. Kark, R., Poskanzer, D., Bullock, J., and Borlen, G.: Mercury poisoning and its treatment with N-acetyl-D,L-penicillamine, N. Engl. J. Med. **285:** 10, 1971.
77. Khera, K., and Tabacova, S.: Effects of methylmercuric chloride on the progeny of mice and rats treated before or during gestation, Food Cosmet. Toxicol. **11:** 245, 1973.
78. Kosta, L., Byrne, A. R., and Zelenko, V.: Correlation between selenium and mercury in man following exposure to inorganic mercury, Nature **254:** 238, 1975.
79. Kurland, L., Faro, S., and Siedler, H.: Minamata disease. The outbreak of a neurologic disorder in Minamata, Japan, and its relationship to the ingestion of seafood contaminated by mercuric compounds, World Neurol. **1:** 370, 1960.
80. Ladd, A. C., Goldwater, L. J., and Jacobs, M. M.: Absorption and excretion of mercury in man. II. Urinary mercury in relation to duration of exposure, Arch. Environ. Health **6:** 480, 1963.
81. Lauwerys, R., and Buchet, J.: Occupational exposure to mercury vapors and biological action, Arch. Environ. Health **27:** 65, 1973.
82. Löfroth, G.: Methylmercury. A review of health hazards and side effects associated with the emission of mercury compounds into natural systems. Radiobiology Division of the Department of Biochemistry, University of Stockholm, and Working Group on Environmental Toxicology, Ecological Research Committee on the Swedish Natural Science Research Council, Stockholm, Sweden, 1969.
83. Lundgren, K., Swensson, Å., and Ulfvarson, U.: Studies in humans on the distribution of mercury in the blood and the excretion in urine after exposure to different mercury compounds, Scand. J. Clin. Lab. Invest. **20:** 164, 1967.
84. Magos, L.: Uptake of mercury by the brain, Br. J. Industr. Med. **25:** 315, 1968.
85. Mansour, M., Dyer, N., Hoffman, L., Davies, J., and Brill, A.: Placental transfer of mercuric nitrate and methyl mercury in the rat, Am. J. Obstet. Gynecol. **119:** 557, 1974.
86. Mansour, M., Dyer, N., Hoffman, L., Schulert, A., and Brill, A.: Maternal-fetal transfer of organic and inorganic mercury via placenta and milk, Environ. Res. **6:** 479, 1973.
87. Matsumoto, H., Koya, G., and Takeuchi, T.: Fetal Minamata disease. A neuropathological study of two cases of intrauterine intoxication by a methyl mercury compound, J. Neuropathol. Exp. Neurol. **24:** 563, 1964.
88. Matsumoto, H., Suzuki, A., and Morita, C.: Preventative effect of penicillamine on the brain defect of fetal rat poisoned transplacentally with methyl mercury, Life Sci. **6:** 2321, 1967.
89. Matsumura, F., Gotch, Y., and Boush, G. M.: Phenylmercuric acetate: Metabolic conversion by microorganisms, Science **173:** 49, 1971.
90. Morikawa, N.: Pathological studies on organic mercury poisoning. II. Experimental production of congenital cerebellar atrophy by bis-ethyl-mercuric sulfide in cats, Kumamoto Med. J. **14:** 87, 1961.
91. Moriyama, H.: [A study on the congenital Minamata disease], J. Kumamoto Med. Soc. **41:** 506, 1967.
92. Murakami, U.: Embryo-fetotoxic effect of some organic mercury compounds, Ann. Rep. Res. Inst. Environ. Med. Nagoya Univ. **19:** 61, 1972.
93. Murakami, U., Kameyama, Y., and Kato, T.: Effects of a vaginally applied contraceptive with phenylmerceric acetate upon developing embryos and their mother animals, Ann. Rep. Res. Inst. Environ. Med. Nagoya Univ. **3:** 88, 1956.
94. Nelson, N. (Chairman), Expert Committee: Hazards of mercury. Special report to the secretary's pesticide advisory committee, Department of Health, Education, and Welfare, Environ. Res. **4:** 1, 1971.
95. Nishimura, H., Hirota, S., Tanaka, O., Ueda, M., and Uno, T.: Normal mercury level in human embryos and fetuses, Biol. Neonate **24:** 197, 1974.
96. Nonaka, I.: An electron microscopical study on the experimental congenital Minamata disease in rats, Kumamoto Med. J. **22:** 27, 1969.
97. Nordberg, G., and Skerfving, S.: Metabolism, *in* Friberg, L., and Vostal, J., editors: Mercury in the Environment. A

Toxicological and Epidemiological Appraisal, PB-205 000, National Technical Information Service, U. S. Department of Commerce, 1971, pp. 4-1 to 4-143.
98. Norseth, T.: Studies of intracellular distribution of mercury, *in* Miller, M., and Berg, G., editors: Chemical Fallout. Current Research on Persistent Pesticides, Springfield, Ill., 1969, Charles C Thomas, Publisher, pp. 408-417.
99. Null, D., Gartside, P., and Wei, E.: Methylmercury accumulation in brains of pregnant, non-pregnant and fetal rats, Life Sci. **12:** 65, 1973.
100. Ordóñez, J. V., Carillo, J. A., Miranda, C., M., and Gale, J. L.: Epidemiological study of an illness in the Guatemala highlands believed to be an encephalitis, Bol. Ofic. Sanit. Panam. **172:** 65, 1971.
101. Pařízek, J., Babický, A., Ošťádalová, I., Kalousková, J., and Pavlík, L.: The effect of selenium compounds on the cross-placental passage of ^{203}Hg, *in* Sikov, M. and Mahlum, D., editors: Radiation Biology of the Fetal and Juvenile Mammal. Proceedings of the Ninth Annual Hanford Biology Symposium at Richland, Washington, May 5-8, 1969. Oak Ridge, Tenn., 1969, U. S. Atomic Energy Commission, pp. 137-143.
102. Pařízek, J., Benes, I., Oštádoalová, I., Babický, A., Benes, J., and Lener, J.: Metabolic interrations of trace elements the effects of some inorganic and organic compounds of selenium on the metabolism of cadmium and mercury in the rat, Physiol. Bohemosiov. **18:** 95, 1969.
103. Philip, A. P. W.: On the Influence of Minute Doses of Mercury Combined with the Appropriate Treatment of Various Diseases, in Restoring the Functions of Health, and the Principles on which it Depends. Washington, D. C., 1834, D. Green.
104. Pitkin, R. M., Bahns, J., Filer, L. J., and Reynolds, W. A.: Mercury in human maternal and cord blood, placenta and milk, Proc. Soc. Exp. Biol. Med. **151:** 565, 1976.
105. Pierce, P., Thompson, J., Likosky, W., Nickey, L., Barthel, W., and Hinman, A.: Alkyl mercury poisoning in humans. Report of an outbreak. J. A. M. A. **220:** 1439, 1972.
106. Pillay, K., Thomas C., Jr., Sondei, J., and Hyche, C.: Mercury pollution of Lake Erie ecosphere, Environ. Res. **5:** 172, 1972.
107. Prescott, L., and Ansari, S.: The effects of repeated administration of mercuric chloride on exfoliation of renal tubular cells and urinary glutamic-oxaloacetic transaminase activity in the rat, Toxic Appl. Pharmacol. **14:** 97, 1969.
108. Ramel, C.: Genetic effects of organic mercury compounds, Hereditas **57:** 445, 1967.
109. Ramel, C.: Genetic effects of organic mercury compounds. I. Cytological investigations on allium roots, Hereditas **61:** 208, 1969.
110. Ramel, C., and Magnusson, J.: Genetic effects of organic mercury compounds. II. Chromosome segregation in *Drosophila melanogaster*, Hereditas **61:** 232, 1969.
111. Rentos, P. G., and Seligman, E. J.: Relationship between environmental exposure to mercury and clinical observation, Arch. Environ. Health **16:** 794, 1968.
112. Reynolds, W. A., and Pitkin, R. M.: Transplacental passage of methylmercury and its uptake by primate fetal tissues, Proc. Soc. Exp. Biol. Med. **148:** 523, 1975.
113. Ringoir, S.: LDH isoenzyme pattern of rat kidney in mercurial intoxication, Nephron **7:** 538, 1970.
114. Selye, H.: Mercury poisonings: Prevention by spironolactone, Science **169:** 775, 1970.
115. Sherrington, Sir Charles: The Endeavour of Jean Fernel. Cambridge, 1946, Cambridge University Press.
116. Siedlecki, J. T.: Diagnosis of exposure to mercury—effect on pregnancy, J. A. M. A. **215:** 648, 1971.
117. Silberg, I., Prutkin, L., and Leider, M.: Electron microscopic studies of transepidermal absorption of mercury. Histochemical methods for demonstrating of electron densities in mercury treated skin, Arch. Environ. Health **19:** 7, 1969.
118. Skerfving, S.: Organic mercury compounds—relation between exposure and effects, *in* Friberg, L., and Vostal, J., editors: Mercury in the Environment. A Toxicological and Epidemiological Appraisal, PB-205-000, National Technical Information Service, U. S. Department of Commerce, U. S. Govt., pp. 8-1 to 8-44, 1971.
119. Skerfving, S.: Mercury in fish—Some toxicological considerations, Food Cosmet. Toxicol. **10:** 545, 1972.
120. Skerfving, S., Hansson, K., and Lindsten, J.: Chromosome breakage in humans exposed to methyl mercury through fish consumption, Arch. Environ. Health **21:** 133, 1970.
121. Skerfving, S., and Vostal, J.: Symptoms and signs of intoxication, *in* Friberg, L., and Vostal, J., editors: Mercury in the Environment. A Toxicological and Epidemiological Appraisal, PB-205-000, National Technical Information Service, U. S. Department of Commerce, pp. 5-1 to 5-47, 1971.
122. Snyder, R. D.: Congential mercury poisoning, N. Engl. J. Med. **18:** 1014, 1971.
123. Snyder, R. D.: The involuntary movements of chronic mercury poisoning, Arch. Neurol. **26:** 379, 1972.
124. Southard, J., Nitisewojo, P., and Green, D. E.: Mercurial toxicity and the perturbation of the mitochondrial control system, Fed. Proc. **33:** 2147, 1974.
125. Spyker, J. M., and Smithberg, M.: Effects of methylmercury on prenatal development in mice, Teratology **5:** 181, 1971.
126. Spyker, J. M., Sparber, S. B., and Goldberg, A. M.: Subtle consequences of methylmercury exposure: behavioral deviations in offspring of treated mothers, Science **177:** 621, 1972.
127. Suzuki, T., Matsumoto, N., Miyama, T., and Katsunuma, H.: Placental transfer of mercuric chloride, phenyl mercury acetate, and methyl mercury acetate in mice, Industr. Health **53:** 219, 1967.
128. Suzuki, T., Miyama, T., and Katsunuma, H.: Comparison of mercury contents in maternal blood, umbilical cord blood, and placental tissues, Bull. Environ. Contam. Toxicol. **5:** 502, 1971.
129. Swensson, Å.: Investigations on the toxicity of some organic mercury compounds which are used as seed disinfectants, Acta. Med. Scand. **143:** 365, 1952.
130. Takahashi, H., Hirayams, K., and Kuroda, T.: Use of pyridoxine-5-thiol in methyl mercury poisoning, Toxic Appl. Pharmacol. **18:** 988, 1971.
131. Takeda, Y., Kunugi, T., Hoshino, O., and Ukita, T.: Distribution of inorganic, aryl and alkyl mercury compounds in rats, Toxic Appl. Pharmacol. **13:** 156, 1968.
132. Takeuchi, T., Kambara, T., and Morikawa, N.: Pathologic observations of the Minamata disease, Acta Pathol. Jap. **9:** 769, 1950.
133. Takizawa, Y.: Studies on the Niigata episode of Minamata disease outbreak, Acta Med. Biol. (Niigata) **17:** 293, 1970.
134. Takizawa, Y., Kosaka, T., and Sugai, R.: Studies on the cause of the Niigata episode of the Minamata disease outbreak, Acta Med. Biol. **19:** 193, 1972.
135. Tanner, J. T., Friedman, M. H., Lincoln, D. N., Ford, L. A., and Jarree, M.: Mercury content of common foods determined by neutron activation analysis, Science **177:** 1102, 1972.
136. Tatetsu, S., and Harada, M.: [Mental deficiency resulting from mercury intoxication in the prenatal period], Adv. Neurol. Sci. (Tokyo) **12:** 181, 1968.

137. Tejning, S.: Kvicksilverhalterna i blodkroppar och i blodplasma hos "normala" mödrar och deras nyfödda barn. Report 680220, Clin. Occup. Med., Univ. Hosp., Lund, Sweden, 1968.
138. Tepper, L. B.: Analytical considerations, *in* Lee, D. H. K., editor: Metallic Contaminants and Human Health, New York, 1972, Academic Press, Inc., pp. 229-241.
139. Thrasher, J. D., and Adams, J. F.: The effects of four mercury compounds on the generation time and cell division in *Tetrahymena pyriformis*, WH14, Environ. Res. **5:** 443, 1972.
140. Vallee, B., and Ulmer, D.: Effects of mercury, cadmium, and lead, Ann. Rev. Biochem. **41:** 91, 1972.
141. Verity, M. A., and Brown, W. J.: Hg^{++}-induced kidney necrosis. Subcellular localization and structure-linked lysosomal enzyme changes, Am. J. Pathol. **61:** 57, 1970.
142. Vostal, J., and Clarkson, T.: Mercury as an environmental hazard, J. Occup. Med. **15:** 649, 1973.
143. Vroom, F., and Greer, M.: Mercury vapour intoxication, Brain **95:** 305, 1972.
144. Wada, O., Toyokawa, K., Suzuki, T., Suzuki, S., Yano, Y., and Nakao, K.: Response to a low concentration of mercury vapor. Relation to human prophyrin metabolism, Arch. Environ. Health **19:** 485, 1969.
145. Wei, E., and Spear, R.: The fatal dose of methylmercury in man. J. A. M. A. **216:** 1347, 1971.
146. Westöö, G.: Methylmercury compounds in animal foods, *in* Miller, M. W., and Berg, G. G., Editors: Chemical Fallout. Current Research on Persistent Pesticides, Springfield, Ill., 1969, Charles C Thomas, pp. 75-90.
147. Wilson, J., and Du Vigneaud, V.: L-Penicillamine as a metabolic antagonist, Science **107:** 653, 1948.
148. Wood, J., Kennedy, F., and Rosen, C.: Synthesis of methyl mercury compounds by extracts of a methanogenic bacterium, Nature **220:** 173, 1968.
149. Yamane, T., and Davidson, N.: On complexing of desoxyribonucleic acid (DNA) by mercuric ion, J. Am. Chem. Soc. **12:** 2599, 1961.
150. Yang, M., Krawford, K., Garcia, J., Wang, J., and Lei, K.: Deposition of mercury in fetal and maternal brain, Proc. Soc. Exp. Biol. Med. **141:** 1004, 1972.
151. Yang, M., Wang, J., Garcia, J., Post, E., and Lei, K.: Mammary transfer of ^{203}Hg from mothers to brains of nursing rats, Proc. Soc. Exp. Biol. Med. **142:** 723, 1973.
152. Yoshino, Y., Mozai, T., and Nakao, K.: Distribution of mercury in the brain and its subcellular units in experimental organic mercury poisonings, J. Neurochem. **13:** 397, 1966.

Erratum

In the article, "The barrel-shaped cervical carcinoma," by Therese Lu, M.D., Milagros A. Macasaet, M.D., and James H. Nelson, Jr., M.D., in the March 15, 1976, issue of the JOURNAL, on page 599, Fig. 3 was printed upside down.

ITEMS

North American Conference on Fertility and Sterility

The U. S. International Foundation for Studies in Reproduction, Inc., will hold its next annual Pan-American Conference on Fertility and Sterility (formally known as the North American Conference on Fertility and Sterility), February 4 to 12, 1977, at the Cerromar Beach Hotel, Dorado Beach, Puerto Rico. For more information, write to: U. S. International Foundation for Studies in Reproduction, Inc., 112-44 69th Ave., Forest Hills, New York 11375. Telephone: (212) 544-7599.

Lalor Foundation Research Fellowship Program for 1977

The Lalor Foundation has announced its 1977 program of postdoctorate grants for research in special areas of mammalian reproductive physiology.

The Foundation will make grants up to $13,500 each to qualified tax-exempt institutions for conduct of approved projects up to one year. Foreign institutions can, in general, achieve a similar eligibility.

The applicant institution has the obligation and freedom to make its own designation of a Lalor Fellow for conduct of the research from among its own personnel or elsewhere. The Fellow designated should have achievement at least equivalent to the Ph.D. or M.D. degree. The upper age limit is 35 years.

Applications are restricted to research projects bearing on: (1) early amniocentesis in fetal development, or other means for detection and evaluation of dysgenic factors or congenital disabilities, and means toward their disposition; or (2) uterine and cervical physiologic phenomena relevant to pregnancy interruption, particularly for second-trimester terminations.

Forms and details for institution application are available from: The Lalor Foundation, 4400 Lancaster Pike, Wilmington, Delaware 19805. Deadline for filing is January 15, 1977. Appointments will be announced March 15, 1977.

Every Physician A Geneticist

"Every Physician A Geneticist," a two-day course on the practical approach to the recognition and management of genetic problems seen in the physician's office, will be presented November 4 and 5, 1976, at Le Quatre Saisons, Montreal, Quebec, Canada. It is sponsored by the Post-Graduate Board for Continuing Medical Education of McGill University and the Montreal Children's Hospital. The course is approved for credits. Fee is $125.00.

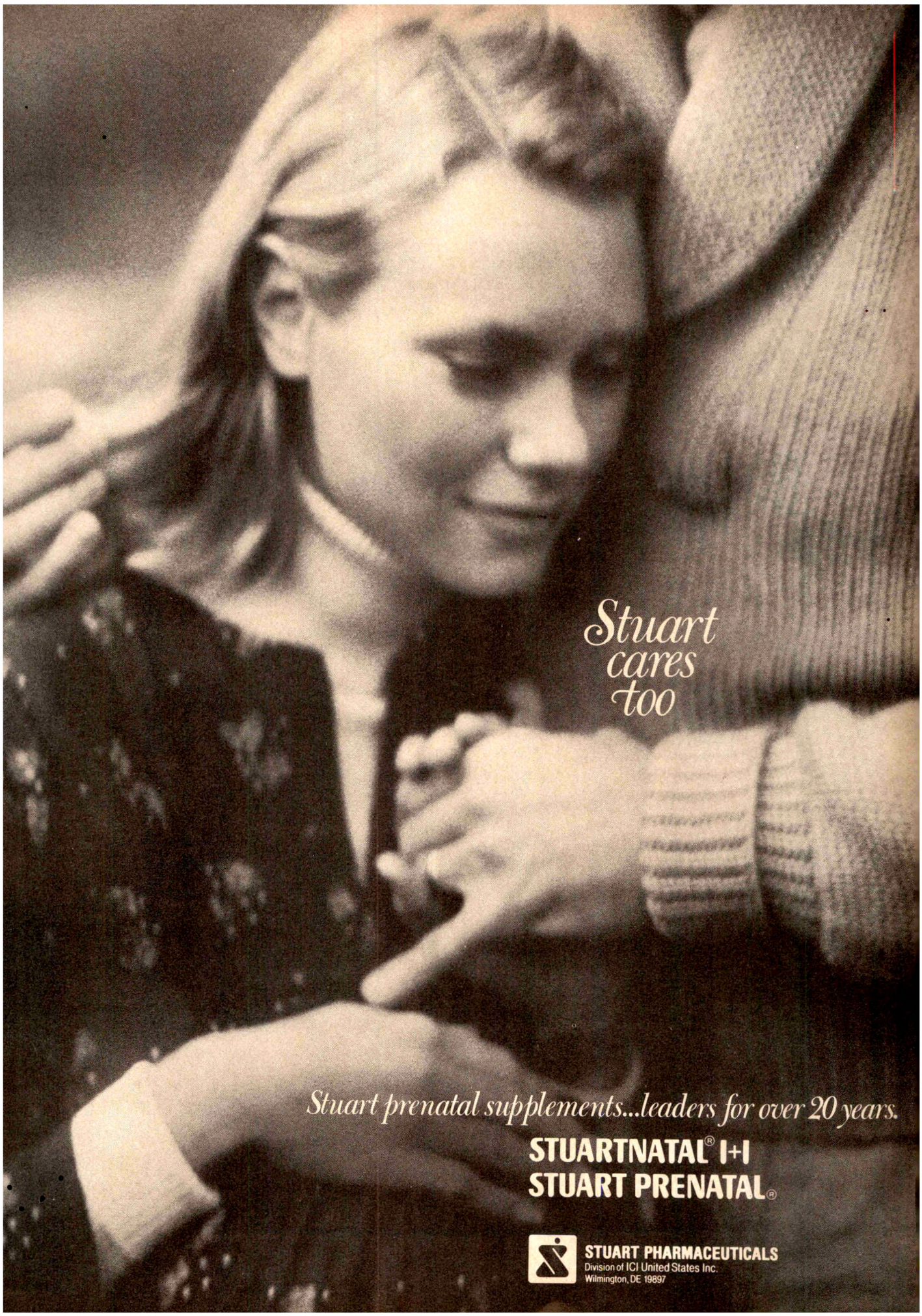
For further information, contact: Dr. H. Goldman, Post-Graduate Board, Montreal Children's Hospital, 2300 Tupper St., Montreal, Quebec, Canada.

The Team Approach to the Care of Burns in Children

A program entitled "The Team Approach to the Care of Burns in Children" will be presented October 8, 1976, at The Children's Hospital, Denver, Colorado, in the Boettcher Auditorium, from 8 A.M. to 4 P.M. For further information and registration, contact: MaryAnn Van Gorp, Department of Continuing Education, The Children's Hospital, 1056 E. Nineteenth Ave., Denver, Colorado 80218. Telephone: (303) 861-8888, Ext. 2280.

Symposium on Treatment of Disorders of the Urethro-Vesical Junction

The Symposium on Treatment of Disorders of the Urethro-Vesical Junction will be held November 10 and 11, 1976, in the Auditorium of the Delaware Academy of Medicine, Lovering Ave. and Union St., Wilmington, Delaware, with presentations by leading investigators and clinicians. The course is approved by the American Medical Association Council on Medical Education in Category 1 for an hour-for-hour contact basis and by the American College of Obstetricians and Gynecologists for 25 cognates. The fee will be $200 for physicians and $50 for residents who have a letter from their Chief of Service. Registration should be made by October 15, 1976, and is on a first-come, first-served basis. For further information, contact: Department of Obstetrics and Gynecology, Wilmington Medical Center, P. O. Box 1951, Wilmington, Delaware 19899.


Stuart
cares
too
Stuart prenatal supplements...leaders for over 20 years.
STUARTNATAL® 1+1
STUART PRENATAL®
STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, DE 19897

Articles to appear in early issues

Controlled trial of fetal intensive care
Peter Renou, Allan Chang, Ian Anderson, and Carl Wood
Melbourne, Victoria, Australia

Blood as a potential vehicle for the cytomegaloviruses
Gilles R. G. Monif, M.D., George I. Daicoff, M.D., and Lynn L. Flory, M.D.
Gainesville, Florida

A prerecorded program for the Ball pelvimetry technique
Emanuel A. Friedman, M.D., Med.Sc.D.
Boston, Massachusetts

Thrombotic thrombocytopenic purpura associated with pregnancy
Harry V. May, Jr., M.D., Guy M. Harbert, Jr., M.D., and W. Norman Thorton, Jr., M.D.
Charlottesville, Virginia

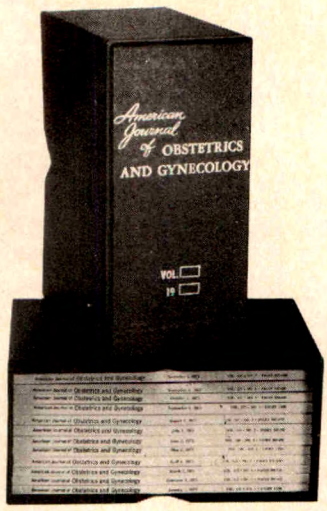
Induction of menstruation with bromocryptine in patients with euprolactinemic amenorrhea
George Tolis, M.D., and Frederick Naftolin, M.D., D.Phil.
Montreal, Quebec, Canada

Untreated endocervical gonorrhea and endometritis following elective abortion
Ronald T. Burkman, M.D., James A. Tonascia, Ph.D., Milagros F. Atienza, M.D., and Theodore M. King, M.D., Ph.D.
Baltimore, Maryland

Nonstressed fetal heart rate monitoring in the antepartum period
France Rochard, M.D., Barry S. Schifrin, M.D., Francoise Goupil, M.D., Helene Legrand, M.D., Josette Blottiere, M.D., and Claude Sureau, M.D.
Paris, France, and Boston, Massachusetts

Plasma testosterone and dihydrotestosterone in ovulatory and anovulatory cycles
M. Yusoff Dawood, M.D., Ch.B., M.Med., M.R.C.O.G., F.A.C.O.G., and Brij B. Saxena, Ph.D.
New York, New York

Familial allergic seminal vulvovaginitis
Te-Wen Chang, M.D.
Boston, Massachusetts



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼" × 11") for 1975 copies
☐ OLD SIZE (7¼" × 10½") for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

ASSISTANT PROFESSOR OF OBSTETRICS & GYNECOLOGY

The Charleston Division of the West Virginia University Medical Center is seeking applications for the position of Assistant Professor in the Department of Obstetrics and Gynecology. Applicant must be board certified, interested in medical students, housestaff, and other health profession training and education. A background of good clinical experiences with special interest in Ob-Gyn Endocrinology is preferable. Qualified and interested applicants should contact Narinder N. Sehgal, M.D., Director, Department of Ob/Gyn, Charleston Division, West Virginia University Medical Center, 3200 MacCorkle Avenue, S.E., Charleston, West Virginia 25304. An Equal Opportunity/Affirmative Action Employer M/F.

Need Chief of Obstetrics-Gynecology for 213 bed hospital/hospital-base group practice. Active resident teaching program associated with University of Arizona. Good salary and benefits. Sunny Tucson. Contact Thomas Corley, Administrator, Kino Community Hospital, 2900 South Sixth Avenue, Tucson, Arizona 85713.

Breast self-examination:

KEY ROLE OF THE PHYSICIAN

item:	**Breast cancer is a major concern of American women, according to a recent Gallup study conducted for the American Cancer Society.**
item:	**Although aware that early discovery improves the chances of cure, and that BSE can lead to early discovery, *fewer than 1 in 5* women practice BSE, and *only half* have an annual breast examination by a physician.**
item:	**Only 35% of all women polled reported that a *physician* had ever raised the subject of breast self-examination, and only 24% had received instruction from the physician on how to do it. Even among women who regularly see a gynecologist, only 34% had been instructed on BSE.**
item:	***But*, among women who received personal instruction from their physicians, the overwhelming majority *(92%)* practiced BSE during the preceding year.**

The Gallup study revealed that, far more important than increasing awareness of breast self-examination, is the problem of inducing women to practice it regularly. The physician plays a key role in this—by teaching women the correct technique, and instilling in them the confidence that will assure their continued practice of BSE.

The American Cancer Society gives major emphasis to breast cancer through research and a vast array of public educational materials, designed to give women life-saving information about the disease. Our latest approach is via a pioneering television film starring Jennifer O'Neill, "Breast Cancer: Where We Are." Where we *will* be in a few years will certainly hinge on our joint efforts.

American Cancer Society®

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY
TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.
A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

GYNECOLOGIC ENDOCRINOLOGIST

Applications are invited for a faculty position for a fully-trained and certified obstetrician-gynecologist with formal training or experience in reproductive endocrinology and/or infertility to join an active, aggressive and productive program. Send complete resume and letters of reference to: James R. Givens, M.D., Director, Div. of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee, Center for the Health Sciences, 800 Madison Avenue, Memphis, Tennessee 38163. An equal opportunity employer.

PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for 12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼″ × 11″) for 1975 copies**
☐ **OLD SIZE (7¼″ × 10½″) for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____

INDEX TO ADVERTISERS

Abbott Laboratories
Fero-Folic-500/Iberet-Folic-500 ——— 44, 45
Ogen ——— 50, 51, 52

Ayerst Laboratories
Dermoplast ——— Fourth Cover
Premarin Vaginal Cream ——— 16, 17, 18

Breon Laboratories Inc.
Fergon ——— 41

Burroughs Wellcome Co.
Empirin Compound with Codeine No. 3 ——— 4

Elscint Inc.
Fetal Lung Maturity Analyzer ——— 40

Hamot Medical Center
Classified ——— 42

Hewlett Packard
8030A Cardiotocograph ——— 1
Seminar ——— 53

Kino Community Hospital
Classified ——— 61

Mead Johnson Laboratories
Ovcon ——— 31, 32, 33, 34

Medsonics, Inc.
Ultrasound Stethoscope ——— 26

Merrell-National Laboratories
AVC ——— 8

Northeast Health Center
Classified ——— 35

Ortho Pharmaceutical Corporation
Dienestrol ——— 2, 3
ModiCon ——— 46, 47, 48

Parke, Davis & Company
Natafort ——— 36, 37
Norlestrin ——— 12, 13, 14

Purdue Frederick Company, The
Betadine Microbicides ——— 38
Betadine Perineal Wash ——— 10
Betadine Vaginitis Regimen ——— 42, 43

Reynolds Industries, Inc., R.J.
Classified ——— 42

Roche Laboratories
Azo Gantanol ——— 26, 27

Roerig, A Division of Pfizer Pharmaceuticals
Geopen ——— 20, 21

Schmid Laboratories, Inc.
Saf-T-Coil ——— 58

Searle & Co., G.D.
Flagyl ——— 66, Third Cover

Sonicaid, Inc.
Fetal Heart Detectors ——— 35

Stuart Pharmaceuticals, Division of ICI United States Inc.
Prenatals ——— 59

Syntex Laboratories, Inc.
Brevicon ——— Second Cover

Thomas, Publisher, Charles C
Books ——— 39

University of Tennessee
Classified ——— 63

Upjohn Company, The
Cleocin Phosphate ——— 54, 55, 56, 57

West Virginia University
Classified ——— 61

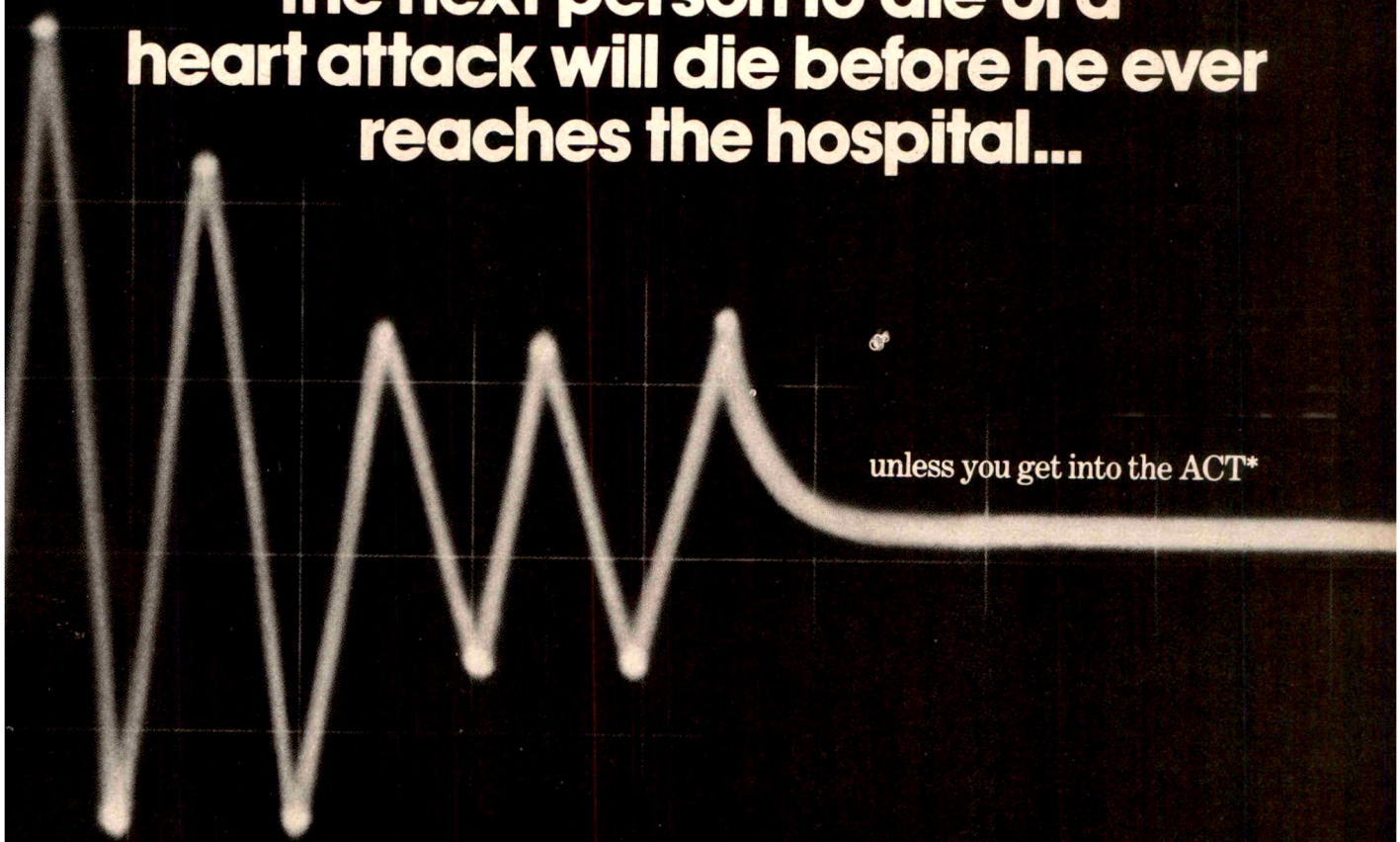
Winthrop Laboratories
Danocrine ——— 22, 23, 24, 25

Wyeth Laboratories
Lo/Ovral ——— 28, 29, 30
Ovral ——— 49

Zeiss, Inc., Carl
Colposcopes ——— 6

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index

Chances are 50/50 the next person to die of a heart attack will die before he ever reaches the hospital...



unless you get into the ACT*

You could be instrumental in bringing Mobile Coronary Care to your community.
We can help you.
We have the facts, figures, and a blueprint for action.
Write us...

***ACT FOUNDATION**
(Advanced Coronary Treatment)
350 Grove Street
Somerville, New Jersey 08876

The ACT Foundation —sponsored as a public service by twelve leading pharmaceutical companies.

ACT Foundation
350 Grove Street
Somerville, New Jersey 08876

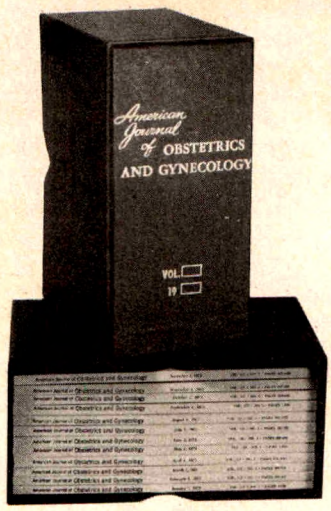
Please send me information on how I can help establish a Mobile Coronary Care System in my community.

Name _____

Address _____

City _____ State _____ Zip _____

D-14084-4



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼" × 11") for 1975 copies**
☐ **OLD SIZE (7¼" × 10½") for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____

Flagyl®

(metronidazole) 250 mg.

Warning

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

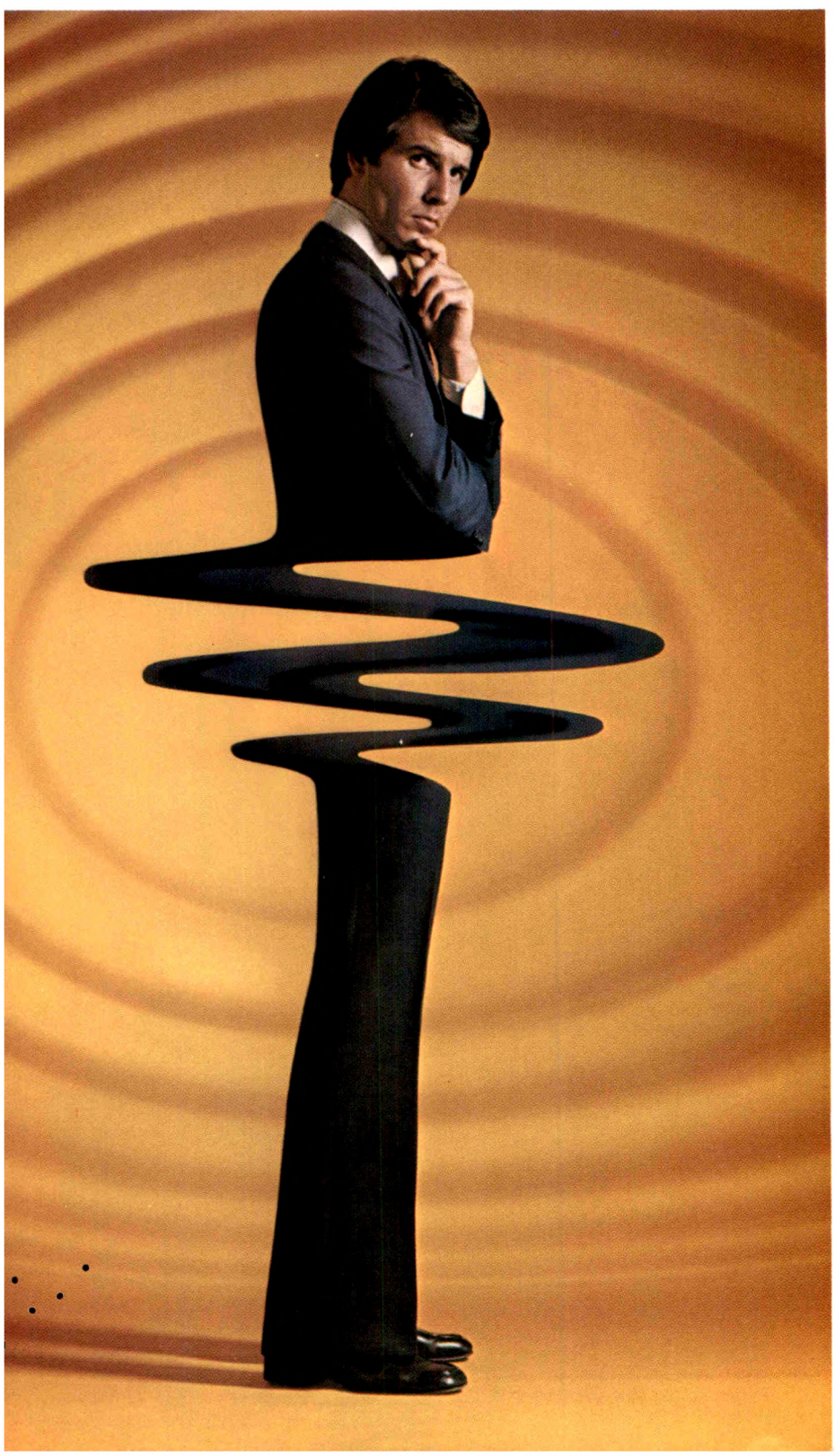
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co.
Medical Department, Box 5110, Chicago, Ill. 60680

If men suffered from the symptoms of trichomoniasis, they'd appreciate Flagyl®.

(metronidazole)



Women with trichomoniasis have been grateful for the benefits of Flagyl therapy for over a decade. Most men have no symptoms and are not even aware that they have contracted trichomoniasis, so they rarely appreciate Flagyl. Unless both sexual partners are diagnosed and treated simultaneously, reinfection from the consort is a probability (the "ping-pong" effect).

In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra and the bladder. Only the systemic action of Flagyl can eliminate trichomonads from these sequestered sites.

In the male, only Flagyl can effectively eliminate trichomonads from the male genitourinary tract.

Thus, for the female Flagyl is the treatment of choice. For the male it is the only choice. And that's something they both can appreciate!

Flagyl®
(metronidazole)
250-mg. tablets

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Please see adjacent page for brief summary of prescribing information.

642

Happy homecoming for the new mother



For continued relief of postepisiotomy discomfort, send her home from the hospital with DERMOPLAST® Aerosol

What DERMOPLAST starts doing to relieve postepisiotomy discomfort in the hospital, it can keep doing at home—to help make the new mother's first days with her baby as enjoyable as they should be. DERMOPLAST permeates the suture line without affecting sutures, and relieves itching that accompanies tissue regeneration and hair regrowth. It will not dry or macerate the skin, and is easily removed with soap and water. DERMOPLAST is easy to apply—sprays from any angle. Available in three sizes, including convenient 3-oz. size that is especially designed for self-administration by the patient.

DERMOPLAST Aerosol Spray contains: Benzocaine, w/w 4.5%; benzethonium chloride, w/w 0.1%; menthol, w/w 0.5%; oxyquinoline benzoate, w/w 1.2%; and methylparaben, w/w 2.0%. Inactive ingredients, vegetable oils and propellant. Also contains 1.9% isopropyl alcohol.

For additional indications, full directions for use, and warnings, see label copy on DERMOPLAST Aerosol Spray can.



Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

7535

27.7.77

October 15, 1976
volume 126, *number* 4

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

Official Publication

AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY



Published by

THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (4) 411-520 (1976)



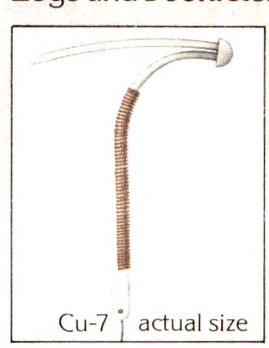
Now, the flexibility you need.

New, improved insertion instrument simplifies accurate fundal placement.

Our Cu-7 insertion instrument has been completely redesigned and engineered to facilitate accurate fundal placement. Using the recommended procedure, Cu-7 positioning can now be accomplished in just seconds, usually with minimal patient discomfort.

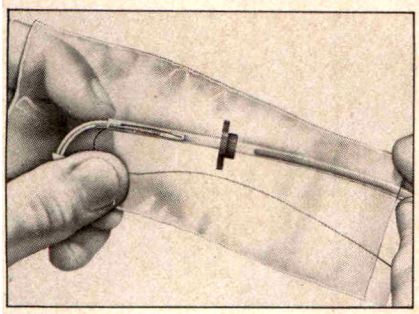
The Cu-7 itself offers reliable, comfortable protection from pregnancy, rivaling "the pill" as a method of choice for nulliparous as well as multiparous women.

Your Searle representative is eager to advise you of the correct steps required for simple insertion of the Cu-7. Please ask for a demonstration—and for Patient Logs and booklets.

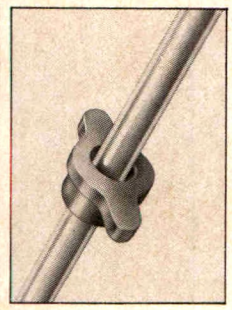


Cu-7®
intrauterine copper contraceptive

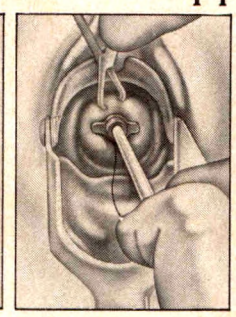
How five newly designed features make it easier to use Cu-7® intrauterine copper contraceptive.



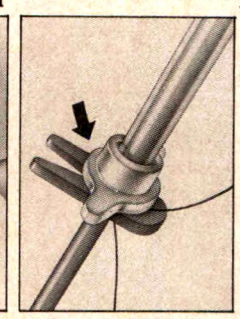
1. New sterile sheath
Helps maintain sterility during loading procedure and cervical-stop setting.



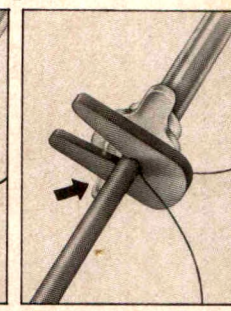
2. New blue-winged cervical stop
A visual guide to aid in correct positioning of the "seven" in the uterus.



3. New flexible rod
Facilitates insertion of "seven" into virtually any normal uterine cavity in seconds.



4. New welded tube-stop
Serves as handle for withdrawing the tube and removal of instrument.



5. New thread-retaining clip
When held to tube-stop during procedure, facilitates insertion and makes tube-crimping virtually impossible.

Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is 89 mg. of pure, virgin electrolytic copper wire providing 200mm^2 of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the copper coil into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication: The Cu-7 is indicated for contraception.

Contraindications: The presence of any of the following, at the time of insertion, constitutes a contraindication: pregnancy, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months, endometrial disease such as hyperplasia or carcinoma and a known or suspected allergy to copper.

Warnings: Recent reports suggest an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. In some cases, initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned of the suggested incidence of increased risk of sepsis and followed with close vigilance.

The long-term effects on the offspring of the presence of copper in the uterus during pregnancy are unknown.

Perforations of the uterus have occurred. In this case the device should be removed immediately.

The use of microwave therapy in patients with metal prosthetics may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients wearing a Cu-7.

Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease, the incidence of which is one in two hundred thousand.

Precautions: A pelvic examination should be done.

Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed shortly following a menstrual period. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed.

Occasional perforations of the uterus (.03%) have been reported, usually during insertion into patients less than two months post abortion or post partum. If penetration into abdominal cavity occurs, laparotomy should be performed and the device recovered. Local inflammatory reaction with abscess formation is a possibility if a device is left in the abdomen.

If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

The Cu-7 should be removed if pelvic infection which is unresponsive to treatment occurs.

The device should be replaced every two years. There is no evidence of decreasing effectiveness with time before two years, but the contraceptive effectiveness of the Cu-7 after two years has yet to be established.

If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to pull on the thread and displace the Cu-7 and told to return in two years for its replacement.

A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman wearing a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being worn.

Adverse Reactions: Perforation of the uterus has occurred.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women.

Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Transient spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. The following complaints have also been reported, although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, and cystitis.

Dosage and Administration: A single Cu-7 is to be inserted into the uterine cavity (see Precautions section). The small diameter of the Cu-7 enables easy insertion into the nulliparous as well as the multiparous uterus. Present information indicates that the efficacy is retained for at least 24 months. Until accurate data indicating a longer effective life become available, the Cu-7 should be removed and a new one inserted on or before 24 months from the date of insertion. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

How Supplied: Available in cartons of 6 and boxes of 30 sterile units (Cu-7 with an inserter) and sufficient patient identification cards.

Clinical Studies: Different event rates have been recorded with the use of different intrauterine contraceptive devices, inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use.) This experience encompasses 321,699 woman-months of use, including 12 months for 9,594 women and 24 months for 7,599.

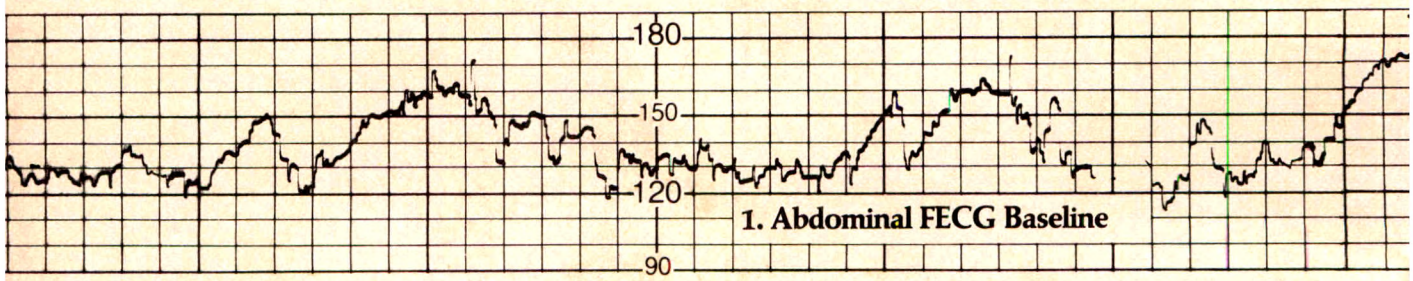
	12 Months		24 Months	
	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.7	1.3	2.5	2.1
Expulsion	5.5	7.7	6.5	8.7
Medical Removal	9.6	12.7	15.3	18.2
Continuation Rate	78.3	72.9	63.9	59.7

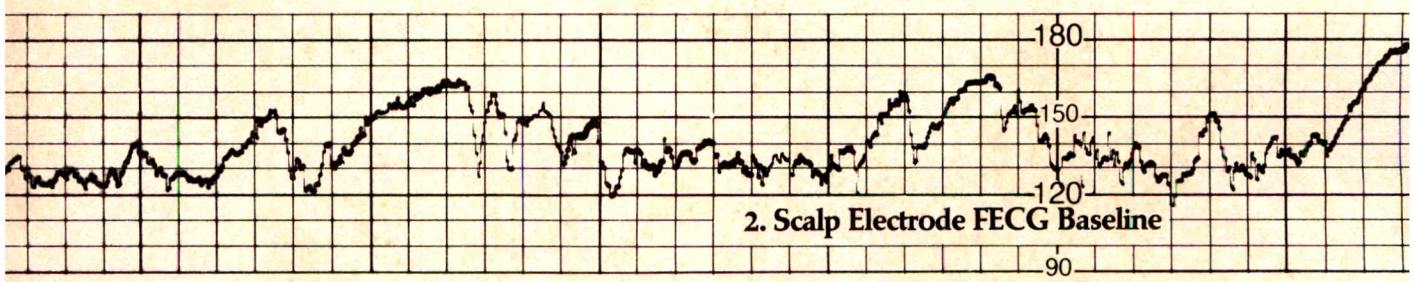
Please see complete product labeling for insertion and removal techniques.

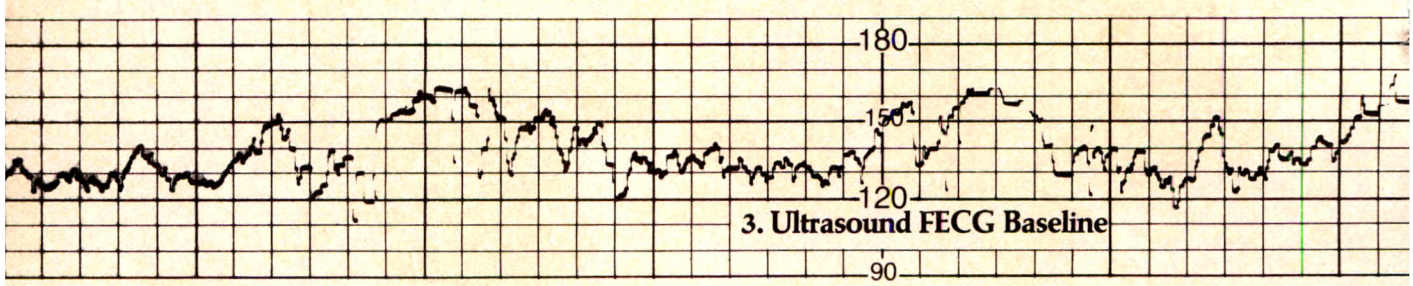
SEARLE **Searle Laboratories**
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

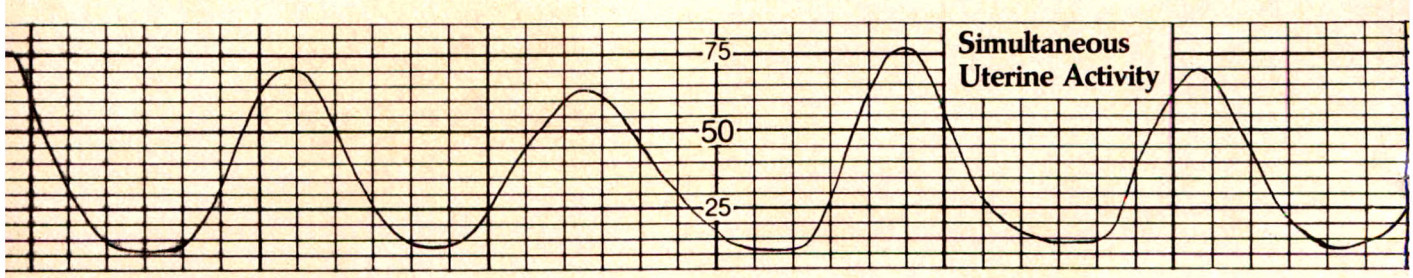
6B1-R1

Happy Birth











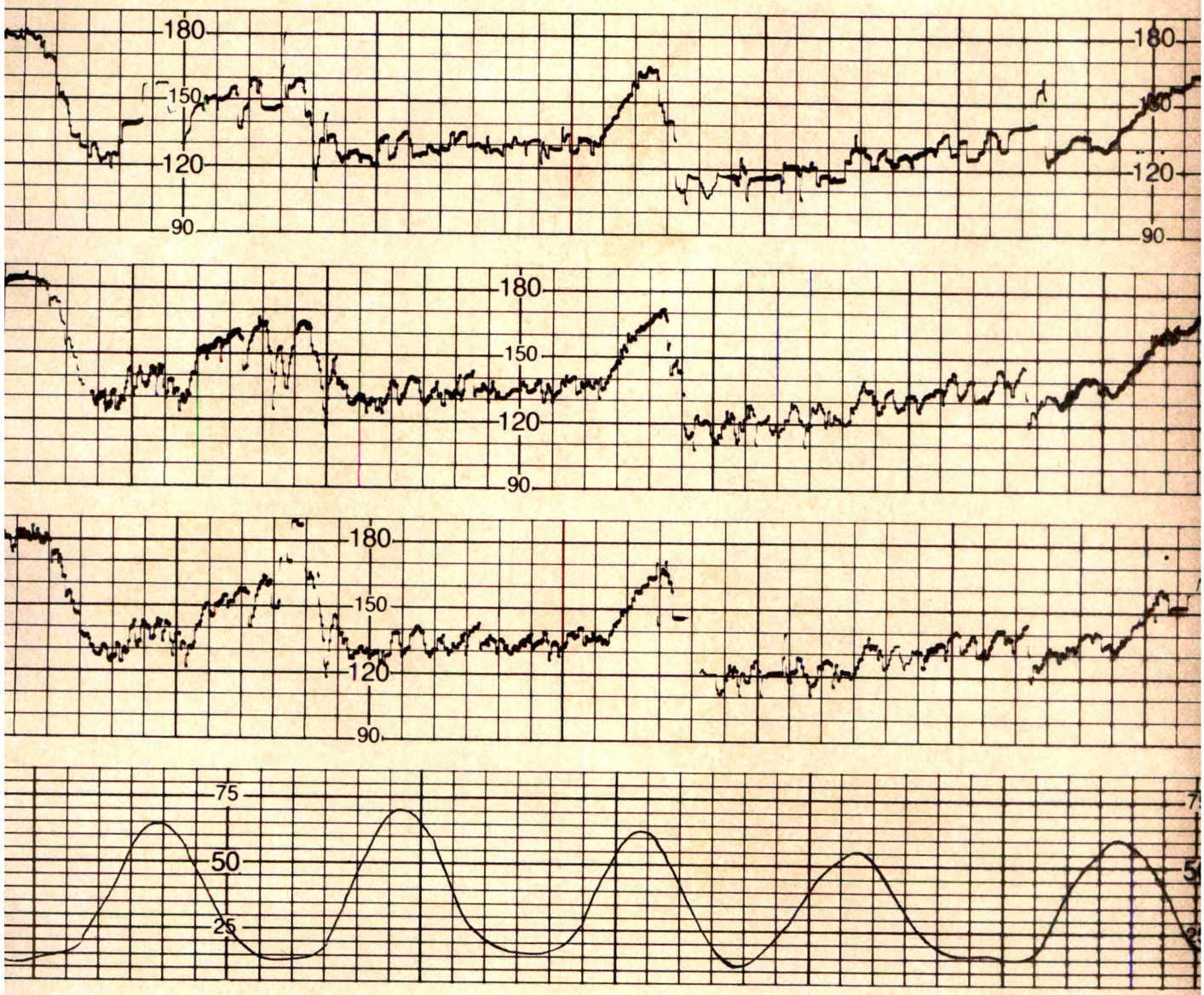
Our new Fetal Monitor offers three ways to observe the occasion.

1. Abdominal FECG—Baseline. For years it was only a promising theory. But the B-D Electrodyne Fetal Monitor solves the difficult problem of separating the maternal heart beat from the fetal heart beat—even when the QRS complexes are merged.

Through over 2,500 hours of labor with more than 500 patients, the B-D Electrodyne abdominal ECG method proved itself applicable, on average, for 3 out of 4 fetal monitoring candidates. As you can see in the recordings, accuracy and performance were remarkably close to that of the directly attached scalp electrode.

The B-D Electrodyne Fetal Monitor records contractions simultaneously from a lightweight tocody-

lays, America!



mometer. Trend, digital display of fetal heart e, and variable speed recorder for FECG and ternal ECG and labor contractions are also luded.

Scalp Electrode FECG—Baseline. After presentan occurs, and if contraction interference becomes ere, this most reliable of methods may be prered. The B-D Electrodyne Fetal Monitor switches ckly to this capability.

Ultrasonic FECG Baseline. Because the physiology some patients occasionally prevents the use of dominal ECG (one out of four cases on average), offer our Ultrasound Amplifier an an option. nsducer and accessories are included.

Altogether the B-D Electrodyne Fetal Monitor gives you the best of three worlds. And B-D Electrodyne's inservice education and warranty policies are among the best. Let us demonstrate at your place. Please write or call and we'll be glad to make arrangements. B-D Electrodyne, Division of Becton, Dickinson and Company, Route One, Sharon, Massachusetts 02067. (617) 828-9080

B-D ELECTRODYNE
Division of Becton, Dickinson and Company

© Copyright 1976 B-D Electrodyne

After 40 years... ...still brand new

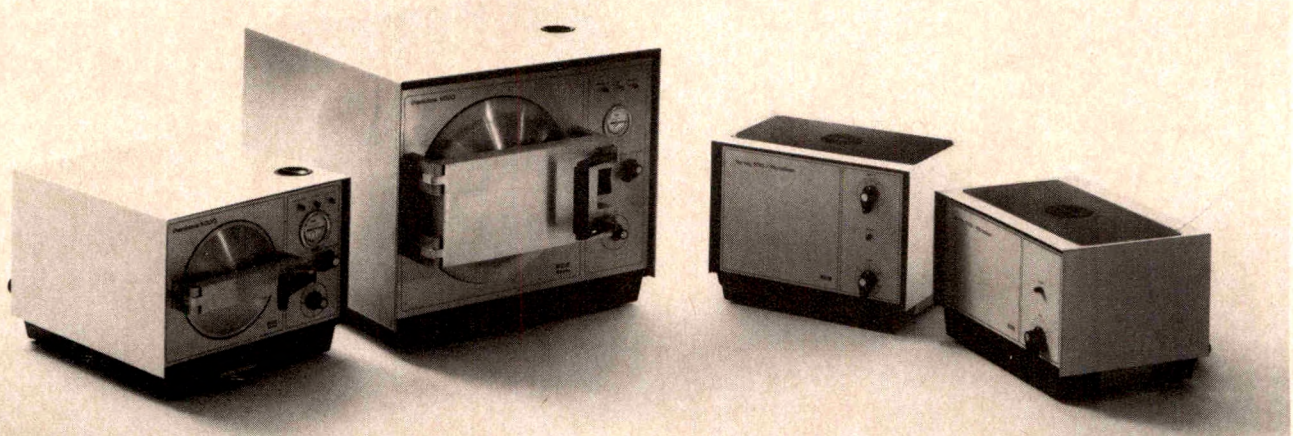
Since 1936 successive models of Harvey sterilizers and ultrasonic cleaners have represented the most advanced sterilization systems available. Today's models are no exception.

The brand new 5000 and 6000 Chemiclaves are the first fully automated Harvey sterilizers. Furthermore, they offer the shortest sterilization cycles ever... just 20 minutes.* And as with previous Harveys, Chemiclaves do not dull cutting edges, rust or corrode instruments, weaken solder joints, remove temper, or saturate or scorch soft goods. The 5000 Chemiclave is primarily for office use, while the larger 6000 Chemiclave is ideal for group practices, clinics, hospitals and institutions.

The 100 and 200 Vibracleans offer features not available on any other ultrasonic cleaners. The 200 Vibraclean even includes variable energy selection. And both models are whisper quiet. The four-quart 100 Vibraclean is large enough for most users. The six-quart 200 Vibraclean is perfect for laboratories and others who require larger capacity.

Send for our complete sterilization systems brochure. After 40 years it's still brand new.

*Exclusive of pressure rise time, which will vary.



MDT®

Chemiclave and Vibraclean are registered trademarks of MDT Corporation.

MDT CORPORATION 13618 SOUTH ALMA AVENUE GARDENA CALIFORNIA 90249 (213)321-4822

put us in your hands®

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

October 15

1976

Clinical opinion

The primary treatment of breast carcinoma 411

Stuart M. Poticha, M.D.

Chicago, Illinois

Decreasing postpartum sexual abstinence time 416

A. Cullen Richardson, M.D., James B. Lyon, M.D.,

Ethel E. Graham, R.N., and Nancy L. Williams, B.S., R.N.

Atlanta, Georgia

Gynecology

Abnormal cervical cytology in the teen-ager: A continuing problem 418

Martin J. Feldman, M.D., E. Michael Linzey, M.D., Elena Srebnik, B.A.,

Deryck R. Kent, M.D., Arthur I. Goldstein, M.D., and Morton Nelson, M.D., M.P.H.

Irvine, California

(Contents continued on page 7)

Vol. 126, No. 4, October 15, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.



Nude by Mario Korbel from Museum Pieces Inc.

True human estrogen replacement

Hormonin
(estriol, estradiol, estrone)

BRIEF SUMMARY: See package insert for full prescribing information.

CHOOSE FROM TWO CONVENIENT ORAL FORMS:

HORMONIN NO. 1 (half strength)	*HORMONIN NO. 2 (full strength)*
Each Tablet Contains:	*Each Tablet Contains:*
ESTRIOL 0.135 mg.	*ESTRIOL 0.27 mg.*
ESTRADIOL 0.3 mg.	*ESTRADIOL 0.6 mg.*
ESTRONE 0.7 mg.	*ESTRONE 1.4 mg.*

INDICATIONS: Replacement therapy for naturally occurring or surgically induced estrogen deficient states, including the menopause syndrome and post-menopausal conditions.

CONTRAINDICATIONS: Women having familial or personal history of mammary or genital cancer.

PRECAUTIONS: Estrogen should not be administered to women with recurrent mastitis or abnormal mammograms except in instances where the physician feels that treatment is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen dependent neoplasia.

The physician should be alert to the earliest manifestation of thrombotic disorders. Should this problem occur, discontinue estrogen therapy immediately. The long range effect of estrogen on nursing infants has not been established.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer of hypercalcemia, estrogen administration should be discontinued. The use of any estrogen in pregnancy is not recommended.

A complete pretreatment physical examination should be performed with special reference to the pelvis and breast. To avoid continuous stimulation of the uterus and breast, cyclic therapy is recommended (3 weeks on medication and 1 week off). Withdrawal bleeding may occur during the one week off medication. If unexplained or excessive vaginal bleeding occurs, the physician should check for the organic pathology.

Pre-existing fibromyomata may increase in size while using estrogen. For this reason, patients should be examined at regular intervals. Treatment with estrogen may mask the onset of the climacteric. Certain liver and endocrine function tests may be affected by exogenous estrogen administration.

DOSAGE: Orally, for the relief of menopausal symptoms, HORMONIN NO. 1, 1 or 2 tablets daily according to severity of symptoms; HORMONIN NO. 2, 1 tablet daily. The initial dosage may be decreased to establish maintenance dosage. To avoid possible continuous stimulation of the breast and uterus, cyclic therapy may be employed. In severe cases, initial therapy may be supplemented with parenteral estrogens.

CARNRICK LABORATORIES

DIV. G. W. CARNRICK CO., 65 HORSE HILL ROAD, CEDAR KNOLLS, N.J. 07927

Contents continued from page 5

Virucidal effect of certain chemical contraceptives on Type 2 herpesvirus 422
Balwant Singh, Ph.D., Bosko Postic, M.D., and John C. Cutler, M.D.
Pittsburgh, Pennsylvania

Induction of menstruation with bromocryptine in patients with euprolactinemic amenorrhea 426
George Tolis, M.D., and Frederick Naftolin, M.D., D.Phil.
Montreal, Quebec, Canada

Plasma testosterone and dihydrotestosterone in ovulatory and anovulatory cycles 430
M. Yusoff Dawood, M.D., Ch.B., M.Med., M.R.C.O.G., F.A.C.O.G., and Brij B. Saxena, Ph.D.
New York, New York

Three-day therapy of vulvovaginal candidiasis with econazole: A multicentric study comprising 996 cases 436
J. A. Balmer, M.D.
Berne and Liestal, Switzerland

Familial allergic seminal vulvovaginitis 442
Te-Wen Chang, M.D.
Boston, Massachusetts

Obstetrics

Blood as a potential vehicle for the cytomegaloviruses 445
Gilles R. G. Monif, M.D., George I. Daicoff, M.D., and Lynn L. Flory, M.D.
Gainesville, Florida

The management of the pregnant patient with idiopathic thrombocytopenic purpura 449
James M. Murray, M.D., Major, USAF, MC, and Robert E. Harris, M.D., Ph.D., Lieutenant Colonel, USAF, MC
Lackland Air Force Base, Texas

Thrombotic thrombocytopenic purpura associated with pregnancy 452
Harry V. May, Jr., M.D., Guy M. Harbert, Jr., M.D., and W. Norman Thornton, Jr., M.D.
Charlottesville, Virginia

Sexual experimentation and pregnancy in young black adolescents 459
Maria Gispert, M.D., and Ruth Falk, Ph.D.
Chapel Hill, North Carolina

(Contents continued on page 9)

THE OFFICE OF CONTINUING EDUCATION
BAYLOR COLLEGE OF MEDICINE
Houston, Texas

announces
its

THIRD BIENNIAL POSTGRADUATE COURSE ON

DISEASES OF THE VULVA AND VAGINA JANUARY 13-15, 1977

Presented by

Department of Obstetrics and Gynecology
Baylor College of Medicine

Program Directors: Dr. Herman L. Gardner,
Clinical Professor
Department of Obstetrics and Gynecology

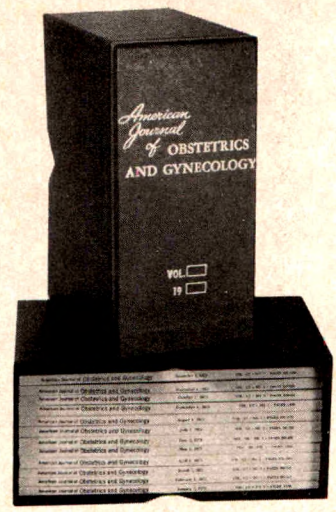
Dr. Raymond H. Kaufman,
Professor and Ernst W. Bertner Chairman,
Department of Obstetrics and Gynecology
and Professor, Department of Pathology

Twenty internationally known physicians including Baylor faculty will conduct a three-day course covering viral infections of the vulva and vagina; the common vulvo vaginitidies; vulvar dystrophies; dermatoses, fungal infections, venereal diseases; and carcinoma in situ and invasive carcinoma. The purpose of the course is to offer registrants a detailed update review of diseases involving these areas.

CONTINUING EDUCATION CREDIT HOURS WILL BE AVAILABLE,

**MARK YOUR CALENDAR NOW—
JANUARY 13-15, 1977**
(Program to be published by November)

For further information contact:
Office of Continuing Education
Baylor College of Medicine
Texas Medical Center
Houston, Texas 77030
(713) 790-4941



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

- -

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼" × 11") for 1975 copies
☐ OLD SIZE (7¼" × 10½") for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

Contents continued from page 7

Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn 467
David Manchester, M.D., Harold S. Margolis, M.D., and Roger E. Sheldon, M.D.
Denver, Colorado

Controlled trial of fetal intensive care 470
Peter Renou, Allan Chang, Ian Anderson, and Carl Wood
Melbourne, Victoria, Australia

A prerecorded program for the Ball pelvimetry technique 477
Emanuel A. Friedman, M.D., Med.Sc.D.
Boston, Massachusetts

Fetus, placenta, and newborn

Sonar biparietal diameter. I. Analysis of percentile growth differences in two normal populations using same methodology 479
Rudy E. Sabbagha, M.D., Franca B. Barton, M.S.,and Bruce A. Barton, M.S.
Chicago, Illinois, and Pittsburgh, Pennsylvania

Sonar biparietal diameter. II. Predictive of three fetal growth patterns leading to a closer assessment of gestational age and neonatal weight 485
Rudy E. Sabbagha, M.D., Bruce A. Barton, M.S., Franca B. Barton, M.S., Elaine Kingas, M.D., Julie Orgill, A.S.U.T.S., and J. Howard Turner, Sc.D.
Chicago, Illinois, and Pittsburgh, Pennsylvania

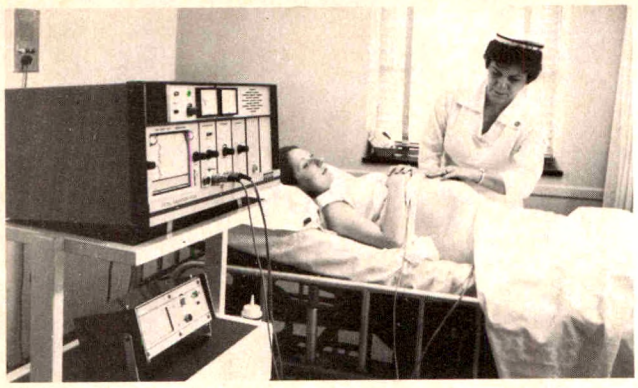
Current practices in antepartum and intrapartum fetal monitoring 491
P. V. Dilts, Jr., M.D.
Memphis, Tennessee

Microcirculation of the rat placenta 495
Mary M. L. Lee and Edward W. Dempsey
New York, New York

Classic pages

Classic pages 506

(Contents continued on page 11)

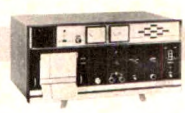


Intensive obstetrical care...

means reliable data on both fetal and maternal parameters from a Sonicaid FM3 monitor. A modular unit, it enables you to design your own ideal fetal maternal monitor. Inputs from both internal and external sources give you excellent flexibility in obtaining data during labor and delivery. Remote, central display links permit multi-patient scanning to optimize personnel use. For complete information, a demonstration, or trial, phone or write Executive Vice President John Scales today.

FM3 Modular Fetal/Maternal Monitor

visual and audio outputs, connections for remote displays and alarms, plus 4 maternal function monitors enable you to create an obstetrical data center for intensive care during labor and delivery.



SONICAID

P.O. Box 714 Fredericksburg, VA 22401 (703)898-6820 Telex 827304

GYNECOLOGIC ENDOCRINOLOGIST

Applications are invited for a faculty position for a fully-trained and certified obstetrician-gynecologist with formal training or experience in reproductive endocrinology and/or infertility to join an active, aggressive and productive program. Send complete resume and letters of reference to: James R. Givens, M.D., Director, Div. of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee, Center for the Health Sciences, 800 Madison Avenue, Memphis, Tennessee 38163. An equal opportunity employer.

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

> *"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."*

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY
TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.
A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

Contents continued from page 9

Communications in brief

An unusual complication of tubal sterilization by silicone rubber banding under laparoscopic vision 507

John M. Esposito, M.D.
Brooklyn, New York

Cytogenetic studies in gonadal dysgenesis with dysgerminoma 508

Antonios Psaroudakis, M.D., Moshe Oettinger, M.D., J. Rogers Byrd, Ph.D., and Robert B. Greenblatt, M.D.
Augusta, Georgia

Gonococcal sepsis secondary to fetal monitoring 510

Haragopal Thadepalli, M.D., Kamalakar Rambhatla, M.D., Jack E. Maidman, M.D., Juan J. Arce, M.D., and Ezra C. Davidson, Jr., M.D.
Los Angeles, California

Gonococcal salpingitis in pregnancy 512

Rene R. Genadry, M.D., Bruce H. Thompson, M.D., and Jennifer R. Niebyl, M.D.
Baltimore, Maryland

Hydatidiform mole and eclampsia with coexistent living fetus in the second trimester of pregnancy 513

Bernard J. Sicuranza, M.D., and Leslie Hughes Tisdall, M.D.
Brooklyn, New York

Iatrogenic intravesical foreign body following Marshall-Marchetti procedure 514

Jan C. Seski, M.D.
Ann Arbor, Michigan

Amylase-containing ovarian cystadenocarcinoma simulating a pancreatic pseudocyst 515

R. R. Joseph, M.D., C. F. Frey, M.D., R. Michaels, Ph.D., and D. S. McCann, Ph.D.
Eloise and Ann Arbor, Michigan

Correspondence

Correspondence 517

Books

• **Books received** 520

(Information for authors on page 19)

(Business communications on page 23)

For the special needs of patients with hard, dry stools

Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT S Tablets offer comfortable relief by softening the stool *and* stimulating its movement.

Provides standardized senna concentrate, a clinically established laxative of choice
Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

Provides DSS, the classic stool softener
DSS in SENOKOT S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime SENOKOT S Tablets usually induce predictable, comfortable evacuation the next morning.

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8339 178576

Senokot® S tablets

(standardized senna concentrate and dioctyl sodium sulfosuccinate)

the "S" stands for softener





Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

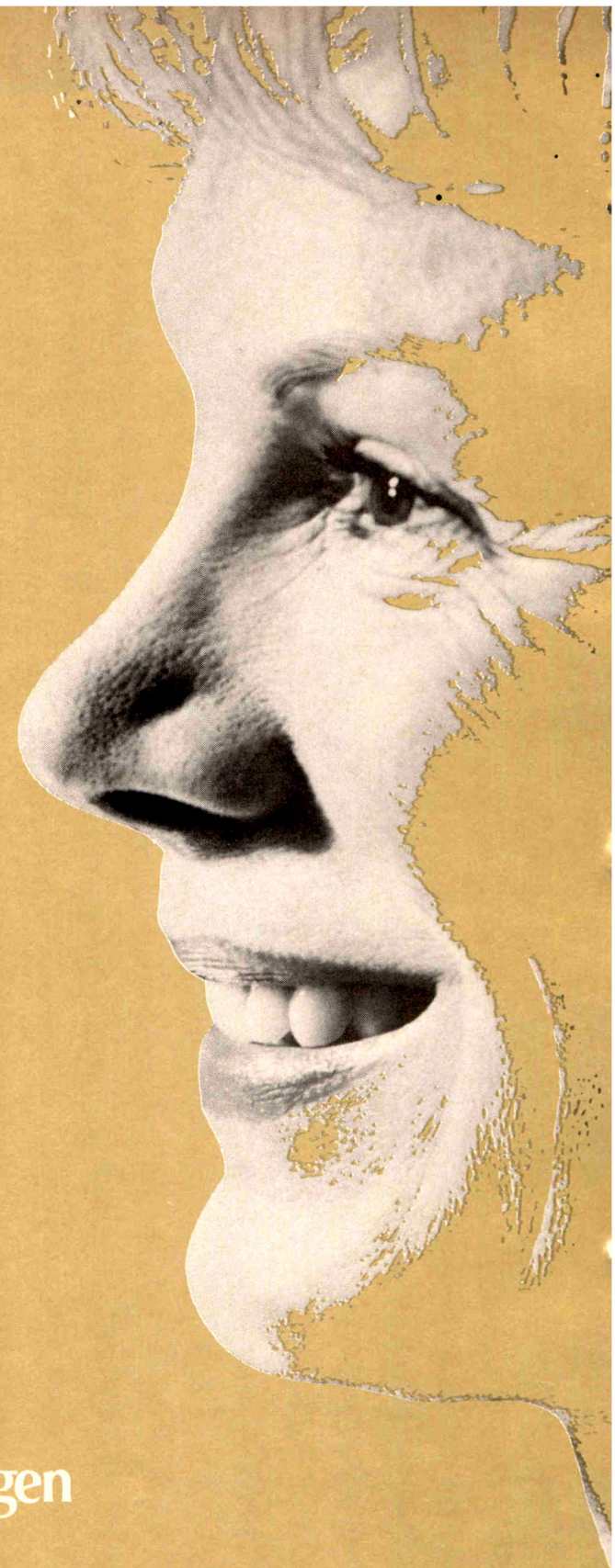
Advisory committee on policy

David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*

Estrogen replacement therapy moves forward



the major human estrogen micronized for oral effectiveness

Estrace®
(estradiol)

1-mg. and 2-mg. scored tablets

- not esterified, not conjugated
- estradiol...the active estrogen at the cellular level

from Mead Johnson

overall, 95% of patients studied gained adequate or complete relief of their symptoms[1]

Estrace (estradiol) was given to 369 estrogen-deficient women for periods ranging up to a year or more (average of six months); 319 of these women received an initial dosage of 1 or 2 mg. per day and were evaluated for efficacy. *Complete disappearance* of hot flushes was experienced by 227 (76%) of 298 women, of sweating by 131 (80%) of 164 women, of tingling by 62 (94%) of 66 women, and of genital atrophy by 44 (88%) of 50 women. In general, 95% of the patients evaluated experienced either adequate or complete relief of their symptoms. Remarkably, in 77% of the patients, symptoms were controlled without need to adjust the initial dosage—usually 2 mg. daily. (Dosage after adjustment ranged from 1 mg. to 3 or 4 mg. a day.)[1]

cyclic therapy recommended

Recently, published reports of retrospective human data have emphasized that patients using estrogens may have an associated increased risk of endometrial cancer. This information makes cyclic rather than continuous estrogen replacement therapy even more prudent. (See brief summary.)

With Estrace, treatment should be initiated with a dose of 1 or 2 mg. daily and then adjusted to the lowest dose possible still maintaining the relief of symptoms. The usual regimen for cyclic administration of Estrace is three weeks on drug, followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4–6 days) to prevent recurrence of menopausal symptoms.

estradiol... orally effective

The technique of micronization has opened up the oral route to natural human estrogen replacement with Estrace. Reduced particle size of the estradiol in Estrace makes effective gastrointestinal absorption possible. Onset of action is rapid, with marked increases in levels of circulating estradiol and estrone; concomitant decreases in serum concentrations of FSH and LH are sustained over a 24-hour period.[2]

Because estradiol can be assayed in plasma, Estrace can provide objective[2] as well as clinical evidence[1] of ready availability and biologic activity.

well accepted by patients[1]

In the 369 patients previously described, the incidence of estrogen-induced side effects with Estrace was relatively low. Incidence of nausea was remarkably low—only 2% of patients before dosage adjustment. Some patients who had complained of this problem while on conjugated equine estrogens reported its complete disappearance on changing to Estrace. Whereas before dosage adjustment 24% experienced breast tenderness, 31% edema, 18% (of 151 with intact uteri) bleeding, and 4% weight gain, only about 2% of the 369 patients dropped out because of side effects.[1]

long-term therapy should be monitored

A few instances of significant gynecologic disease became apparent during clinical investigations.[1] Endometrial hyperplasia was discovered in seven patients, all of whom had previously received estrogen therapy for one to three years prior to entering the study. One patient was reported to have carcinoma *in situ* and another showed adenocarcinoma of the endometrium. In clinical practice, the physician should be alerted to the potential of thrombotic disorders and be prepared to discontinue medication immediately if they occur. Because of variations in normal endogenous hormone production, certain patients may exhibit signs of excessive estrogenic stimulation. Adverse reactions generally associated with estrogen administration may occur and these are listed in the brief summary. Prior to initiation of treatment with Estrace or any other estrogenic preparation, an adequate physical examination should be given.

References

1. Callantine, M.R., *et al.*: Micronized 17β-estradiol for oral estrogen therapy in menopausal women, Obstet. Gynecol. *46*:37–41 (July) 1975.
2. Yen, S.S.C., *et al.*: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β-estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. *40*:518–521 (March) 1975.

For Brief Summary, please see following page.

Estrogen replacement therapy moves forward...

Estrace® (estradiol)

the major human estrogen micronized for oral effectiveness



Indications: Estrace® (17β-Estradiol) is indicated for relief of endogenous estrogen deficiency and associated menopausal symptoms.

Contraindications: Estrace® is contraindicated in patients with 1) markedly impaired liver function; 2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible; 3) known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium; 4) undiagnosed abnormal genital bleeding; 5) thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions; and 6) pregnancy.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen medication should be stopped. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

Adverse Reactions: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis). The following adverse reactions are known to occur in patients receiving estrogens: nausea, vomiting, anorexia, gastrointestinal symptoms (such as abdominal cramps or bloating), edema, breakthrough bleeding, spotting or withdrawal bleeding, breast tenderness and enlargement, change in body weight (increase or decrease), headache, increased cervical mucus, allergic rash, loss of libido and gynecomastia in the male, reactivation of endometriosis, aggravation of migraine headaches, hepatic cutaneous porphyria becoming manifest, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, cystitis-like syndrome, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, possible diminution in lactation when given immediately post-partum, irritability, and malaise.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than non-users to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study. In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients. Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued. It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Childbearing Age. Brit. Med. J., 2:193-199, 1968. (3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969. (5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970. (6) Herbst, et al. — Adenocarcinoma of the Vagina — New England Journal of Medicine, Vol. 284, Number 16 (April 22, 1971).

Dosage and Administration: Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol. Dosage may be adjusted to control the presenting symptoms depending on the response of the individual patient; the minimal effective dose for maintenance therapy should be determined by titration. To avoid continuous stimulation of the reproductive tract and breasts, cyclic therapy is recommended. The usual regimen consists of three weeks on drug followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4-6 days) to prevent recurrence of menopausal symptoms. Withdrawal bleeding of unusual amount or duration should be investigated.

How Supplied: Estrace® 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace® 2 mg; turquoise scored tablets, NDC 0087-0758-01, bottles of 100.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. MJL 5-4127

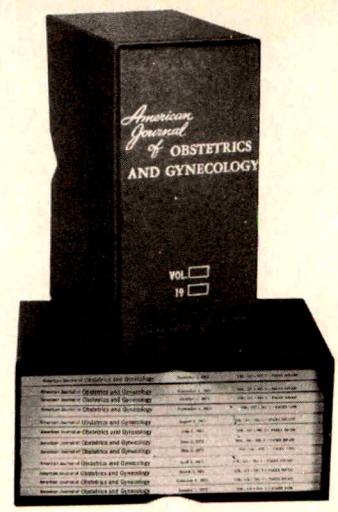
American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS
AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY

The University of Michigan Medical School is seeking a physician to assume the chair of its Department of Obstetrics and Gynecology. Qualifications include: outstanding clinical competance with proven abilities in teaching, research, and scholarship; sufficient national stature to recognize and respond to the future directions of health care delivery in this country; appreciation of the unique doctor-patient relationship in Obstetrics and Gynecology and sensitivity to the psychological needs of women; previous administrative experience and an unequivocal interest in the administration of an academic department. Respond to: Dr. Robert P. Kelch, Chairman, Obstetrics and Gynecology Search Committee, F2428 C.S. Mott Children's Hospital, Department of Pediatrics, The University of Michigan Medical School, Ann Arbor, MI 48109. *A Nondiscriminatory Affirmative Action Employer.*

Board Certified/Eligible Ob-Gyn for young multispecialty group near Syracuse, New York. Full time employment, competitive salary (according to qualifications) plus incentive and fringe benefits. Call Collect, 315-638-0259, Dr. Jeffrey Kaplan, Medical Director.



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼" × 11") for 1975 copies**
☐ **OLD SIZE (7¼" × 10½") for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____

American Journal of Obstetrics and Gynecology
Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2,* Current Investigation and Clinical Opinion, limited to *6,* and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

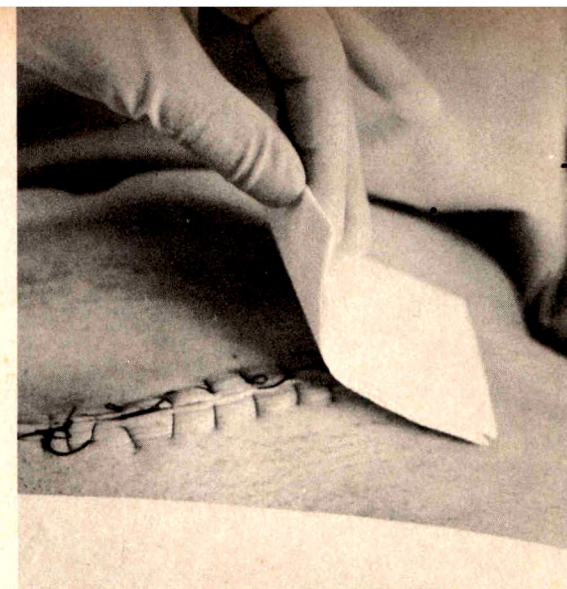
Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Surgical Menopause:

The sign...



The scar is obvious, but the chief concern of every premenopausal woman facing bilateral oophorectomy is that somehow, suddenly, she must face what might have been years away: the symptoms of the menopause.

For many women this fear is a real one, because surgical removal of the ovaries may bring about the abrupt onset of menopausal symptoms: hot flushes, sweats, palpitations, globus hystericus, and other symptoms due to estrogen deficiency. Moreover, such symptoms are often more severe than those that accompany the gradual estrogen decline of the physiological menopause.

Relief can be prompt. For most women, estrogen replacement with PREMARIN (Conjugated Estrogens Tablets, U.S.P.) can begin shortly after surgery—right in the hospital. PREMARIN can minimize the intensity and duration of vasomotor symptoms such as flushes and sweats, and help tide the patient over this distressing period of physiologic adjustment.

Relief can be long-term. Continued on a cyclic basis after discharge, at minimum effective doses, PREMARIN may help retard or prevent many of the long-term sequelae of estrogen deprivation, particularly genital tissue atrophy and osteoporosis.*

PREMARIN. When the menopause is premature...and when it isn't.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.


without
the
symptoms
for surgically-induced
menopausal symptoms
PREMARIN®
(CONJUGATED ESTROGENS
TABLETS, U.S.P.)
CONTAINS
NATURAL
ESTROGENS
EXCLUSIVELY
See next page for Prescribing Information,
Including Revised Warnings Information.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN® Brand of
CONJUGATED ESTROGENS TABLETS, U.S.P.

Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration; however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al.*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)
No. 865—Each *purple* tablet contains 2.5 mg, in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg, in bottles of 100 and 1,000.

References: 1. Smith, D.C., Prentice, R., Thompson, D.J., and Herrmann, W.L.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. 293:1164-1167, 1975. 2. Ziel, H.K., and Finkle, W.D.: Increased risk of endometrial carcinoma among users of conjugated estrogens, N. Engl. J. Med. 293:1167-1170, 1975. 3. Mack, T.M., Pike, M.C., Henderson, B.E., Pfeffer, R.I., Gerkins, V.R., Arthur, M., and Brown, S.: Estrogens and endometrial cancer in a retirement community, submitted for publication.
7637

Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

Estrogen replacement when it's needed most

PREMARIN®

BRAND OF

CONJUGATED ESTROGENS TABLETS, U.S.P.

contains natural estrogens exclusively

American Journal of Obstetrics and Gynecology
Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Editors Emeritus

Howard C. Taylor, Jr.
200 E. 66th St., New York, New York 10021

Allan C. Barnes
111 W. 50th St., New York, New York 10020

Publisher

The C. V. Mosby Company
11830 Westline Industrial Drive
St. Louis, Missouri 63141

Entered at the Post Office at St. Louis, Mo., and additional mailing offices as Second-class matter.

Business communications

Business communications. All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the Publisher, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Publication order. The semimonthly issues of this Journal form three volumes per year; the index is in the last issue of the volume—in the April 15, August 15, and December 15 issues.

Change of address notice. Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, the name of this Journal, and the full form of both old and new addresses, including the ZIP code number.

Advertisements. Forms close 25th of second previous month for the 1st of month issue; 15th of preceding month for the 15th of month issue. Advertising rates and page sizes will be given on application. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Bound volumes. Publishers' Authorized Bindery Service, 4440 West Roosevelt Road, Chicago, Illinois 60624, will quote prices for binding complete volumes in permanent buckram.

Published semimonthly

Subscriptions may begin at any time.


Because
you want more
for her
than just
symptomatic
relief...

Sultrin
TRADEMARK

Triple Sulfa Cream/Vaginal Tablets

effective against and specific for H. vaginalis

The cause of over 90% of "nonspecific" vaginitis†

effective

based on review by the National Academy of Sciences/National Research Counsel, Sultrin was rated as "effective" against *H. vaginalis*.

prompt symptomatic relief

often within a few days, patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

versatile adjunct in other vaginitides

Sultrin is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

convenient choice of dosage forms

Sultrin comes as a soothing, non-staining and esthetically pleasing cream or convenient vaginal tablets.

Composition: Each SULTRIN Tablet contains sulfathiazole 172.5 mg, sulfacetamide 143.75 mg, and sulfabenzamide 184.0 mg. SULTRIN Triple Sulfa Cream contains sulfathiazole 3.42%, sulfacetamide 2.86%, sulfabenzamide 3.7% and urea 0.64%.
Indications: SULTRIN Tablets and Cream are indicated for treatment of *Haemophilus vaginalis* vaginitis. They may also be used as a deodorant for saprophytic infection following radiation therapy.
Contraindications: Sulfonamide sensitivity and kidney disease.
Dosage: SULTRIN Tablets: One tablet intravaginally before retiring and again in the morning for ten days. This course may be repeated if necessary. SULTRIN Cream: One applicatorful intravaginally twice daily for 4 to 6 days. The dosage may then be reduced one-half to one-quarter.
Supplied: SULTRIN Tablets are available in packages of 20 foil-wrapped tablets with vaginal applicator. SULTRIN Cream is available in 2.75 oz. (78 g) tubes with the ORTHO* Measured-Dose Applicator. OJ 10-6 *TRADEMARK

Gardner, H.L. and Kaufman, R.H.:
Benign Diseases of the Vulva and Vagina, St. Louis,
The C.V. Mosby Company, 1969, p. 191.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Ortho





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll, R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. *3*:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 4 OCTOBER 15, 1976

CLINICAL OPINION

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to six citations. Mail to Frederick P. Zuspan, M.D., Editor.

The primary treatment of breast carcinoma

STUART M. POTICHA, M.D.

Chicago, Illinois

The major contributions in the surgical management of carcinoma of the breast have been reviewed. Deficits in our current knowledge have been pointed out in an effort to separate fact from theory and so help the surgeon in choosing the best operation for a patient with breast cancer.

THE PRIMARY treatment of breast carcinoma continues to be the subject of debate and controversy. Recent articles in both the medical and lay press have shaken traditional concepts, making it difficult for physicians to determine the proper treatment for a carcinoma of the breast. This indecision among physicians is further reflected in the growing number of patients who are reluctant to accept radical therapy.

In this maze of conflicting views, how does the clinician reach a justifiable conclusion? The medical literature abounds with studies on the management of breast carcinoma and each method of therapy is supported by survival statistics. Although the strong advocate of a particular type of surgery can point out slight differences in both the 5 and 10 year survival rates by carefully selecting certain papers from the literature, the evidence so obtained cannot justifiably be used to prove the value of one procedure over another.

A better understanding of the dilemma which faces the surgeon may be obtained by reviewing the major contributions in the treatment of carcinoma of the breast. In analyzing each procedure and the scientific evidence which supports it, the clinician begins to recognize what facts are known and what important questions remained unanswered. With this information, he may then plan a logical course of action in treating a patient with primary carcinoma of the breast.

In 1890, William Stewart Halsted,[1] reporting in the *Bulletin of the Johns Hopkins Hospital,* described an operation for the treatment of carcinoma of the breast which consisted of removing the entire breast, a liberal quantity of skin, all of the subcutaneous fat immediately overlying the breast tissue, the pectoralis major muscle (in later descriptions, the pectoralis minor muscle was also included), and all of the axillary fat and lymphatics.

The justification for such an extensive operation can be better appreciated when one considers Halsted's concepts of the pathophysiology of metastasis from breast carcinoma. Halsted believed that metastases from carcinoma of the breast were rarely disseminated through the venous system. He referred to Handley's[2] theory of centrifugal lymphatic spread in stating, "cancer of the breast . . . preserves in the main continuity with the original growth and before involving

Reprint requests: Stuart M. Poticha, M.D., 303 E. Chicago Ave., Chicago, Illinois 60611.

the viscera may become widely diffused along surface planes." Halsted's radical operation was based on the premise that cure of even advanced carcinoma of the breast could be achieved by removal of the breast and all of its contiguous lymphatics. He[3] further postulated, ". . . so it is conceivable that ultimately, when our knowledge of the lymphatics transversed in cases of femur involvement become sufficiently exact, amputation at the hip joint may seem indicated."

In 1907, Halsted[3] reported the results of his operation. The cure rate with negative axillary nodes was 70 per cent and his over-all cure rate was 53.6 per cent of 210 cases. This operation became the unquestioned standard treatment for carcinoma of the breast for the next 50 years.

Although some surgeons have argued that Halsted's reputation made others reluctant to question his operation, such criticism is unjustified. Undoubtedly, the first and most important reason for the success of this procedure was that Halsted was able to cure 50 per cent of women with carcinoma of the breast, whereas prior to his operation very few had been cured. Halsted stated that, ". . . in this country at least a number of the leading surgeons of the generation prior to mine made the pronouncement that they had not in their lifetime cured a single case of breast cancer."

Second, radical mastectomy was associated with remarkably reproducible results. It was not an operation which could be successfully performed only at the Johns Hopkins Hospital. Other surgeons using this technique in centers throughout the world soon reported similar results.

Third, the operation was safe. Halsted's hospital mortality rate was only 1.7 per cent.

In the 1940's, several investigators began to question whether a radical mastectomy was the best operation for all women with carcinoma of the breast. This challenge to such a traditional concept proceeded along several lines.

Many surgeons concentrated their investigative efforts on refining the criteria for operability so as not to subject incurable women to extensive surgery. The most notable studies in this regard are those of Haagensen and Stout.[4] Beginning in 1943[4] and culminating in 1959[5] with a triple biopsy, Haagensen and his co-authors accurately defined operability in breast carcinoma. This screening technique included apical axillary nodes and the internal mammary nodes in the first and second interspaces in addition to biopsy of the primary tumor. In this series of highly selected women treated by radical mastectomy, the 5 year survival rate was 85 per cent.[6]

As a corollary to this work, Haagensen and Cooley[6] also described precise clinical criteria for classifying carcinoma of the breast. An accurate means of describing breast tumors is essential to the surgical management of this disease. Certainly, if a surgeon is to gain any knowledge from the reports of others, he must know the precise nature of the tumors they are operating upon. The Columbia Classification described by Haagensen is one of the most popular systems currently used to classify breast carcinomas; others include the American system, the International system, and the Manchester system. While the differences in these classification systems are determined by size of the primary tumor or the axillary metastasis, the major features are similar. Stage A, or Stage 1, consists of carcinoma confined to the breast alone without any of the grave signs of extensive malignancy. Stage B, or Stage 2, consists of a similar primary tumor with palpable axillary lymph nodes. Stage C, or Stage 3, consists of a tumor which has one or more of the grave prognostic signs of advanced carcinoma, namely edema involving more than one third of the breast, fixation of the primary tumor to the chest wall, axillary lymph nodes greater than 2.5 cm. in diameter, or axillary lymph nodes fixed in the axilla. Stage D, or Stage 4, consists of patients with distant metastasis.

A second group of investigators began to explore the advisability of extending the operation to include lymphatics not encompassed in the standard radical mastectomy. Although 119 of the 232 patients in Halsted's original series underwent a neck dissection, this part of the operation was eventually discontinued. Renewed interest in extended operations, which included resection of the supraclavicular lymph nodes and resection of the internal mammary lymph nodes with or without resection of part of the chest wall, was stimulated by the work of Wagensteen,[7] Kaae and Johansen,[8] Dahl-Iversen and Tofiassen,[9] and Urban.[10]

In general, these operations were accompanied by an increase in morbidity and mortality rates while not improving the survival rate to any appreciable degree. For the most part, these operations have again been abandoned. Some investigators still feel that the Urban operation, which removes the internal mammary lymph nodes, is indicated in patients with centrally located carcinomas or carcinomas arising in the inner quadrants of the breast. They reason that the increased morbidity is justified in these patients because of the high incidence of internal mammary node metastasis found with these lesions.

Simultaneously, other investigators began to examine the advisability of performing less extensive operations for the treatment of primary carcinoma of the breast. These less radical procedures included

modified radical mastectomy, simple mastectomy, and subtotal mastectomy (lumpectomy) with or without irradiation.

In 1948, Patey and Dyson[11] described an operation which differed from the standard radical mastectomy in that the pectoralis major muscle was not removed. This operation was based on the studies of Gray,[12] which showed that the pectoral fascia was a plane practically devoid of lymphatics, suggesting that lymphatics from the breast did not transgress the pectoral muscles en route to the axillary nodes. He reasoned that if the pectoral fascia could be stripped from the pectoral muscles and adequate axillary dissection could be done, the operation would be as successful as radical mastectomy and less deforming. The objections to this modified radical mastectomy were that exposure of the apex of the axilla was difficult and the axillary dissection would be less complete, the pectoralis major muscle would be denervated, and local recurrences would be increased. Subsequent reported series have shown that the innervation of the pectoralis major can be preserved, that local recurrences are not increased, and the 5 and 10 year survival statistics are the same as those reported for radical mastectomy. Even if this operation resulted in a less complete dissection of the apex of the axilla, it would be unlikely that this would be reflected by a decrease in patient survival, since, as Auchincloss[13] has shown, if a patient has more than four axillary lymph nodes involved, and especially if the apical axillary lymph nodes are involved, the prognosis is extremely poor anyhow.

An even less extensive procedure for treatment of carcinoma of the breast is simple mastectomy combined with postoperative irradiation. In 1948, McWhirter[14] published his results on a large series of women treated in this manner. McWhirter pointed out that surgical removal of the axillary contents is unnecessary if these tissues are not invaded by tumor and that, when they are involved, radical mastectomy often fails to cure the patient. Because of these facts, he reasoned that a new approach was justified. McWhirter was able to achieve a 50 per cent 10 year survival rate in his patients using simple mastectomy and radiotherapy. This over-all survival rate compared favorably with the results achieved by radical mastectomy.

McWhirter's work has been criticized because some of his results were extrapolated to 5 year survivals, his dose of irradiation varied, some of his patients were subjected to oophorectomy, and some patients with persistent disease were treated with hormones.

These criticisms notwithstanding, other investigators have subsequently reported large series of patients treated by simple mastectomy and irradiation.[15–17] In some of these series, patients have been retrospectively compared with similar patients treated by radical mastectomy. While such studies are subject to the criticisms of any retrospective analysis, for the most part they tend to support the concept that both the 5 and 10-year survival rates for patients treated by simple mastectomy and irradiation are not statistically different from the rates of those treated by radical mastectomy.

The least aggressive approach for dealing with a primary carcinoma of the breast is that of removing only the mass in the breast. Renewed interest in the so-called lumpectomy operation began with the report of Adair[18] in 1943. He utilized partial mastectomy in treating 53 patients, many of whom received preoperative and/or postoperative irradiation. The 5 year survival rate in these patients was 70 per cent. Several authors have studied large groups of patients treated by lumpectomy and postoperative x-ray therapy. The best results are those reported by Mustakallio.[19] His series contained 127 patients with Stage 1 breast carcinoma. Eighty-four per cent of these patients survived for 5 years, with 72 per cent surviving 10 years. Crile and associates[20] recently have reported a series of 53 patients with 5 and 10 year survival rates of 77 and 34 per cent, respectively.[20]

These alternate methods of therapy for primary breast carcinoma received further impetus with our increased knowledge of tumor biology. The universally accepted fact that the presence of tumor in regional nodes reduces the survival rate led to a classic concept of tumor dissemination. A malignant tumor remains confined to its primary site for a period of time. When it metastasizes, it spreads first to the regional lymph nodes and, after a period of growth there, disseminates further to other locations. Thus, the principle of removing the primary growth in continuity with its lymphatic drainage would appear to offer the patient the best chance of cure.

We now know that the progression of the malignant tumor is not this simple. If it were true that breast carcinoma grew first in the regional nodes before dissemination, then all patients with negative lymph nodes should be cured of the disease. This is not the case, since 10 to 15 per cent of the patients with negative lymph nodes still succumb to the disease.

Furthermore, Handley[21] showed that more than 50 per cent of patients with inner quadrant and centrally located breast carcinomas who have positive axillary nodes also have positive internal mammary nodes, whereas positive internal mammary nodes are found in only 18 per cent of patients with outer quadrant lesions. If patients with central or inner quadrant carcinomas were subjected to a standard radical mas-

tectomy, tumor would remain behind in the internal mammary nodes in more than 50 per cent of the cases. If this tumor subsequently metastasized to other parts of the body, the cure rate for cental and inner-quadrant lesions should be much less than that for outer-quadrant lesions. Evidence seems to indicate that the survival rate in patients subjected to radical mastectomy is not influenced by the location of the primary tumor.

Studies such as this have led investigators to reappraise this concept of tumor dissemination. The absence of tumor within lymph nodes may not mean that the tumor cells have remained confined to the primary growth, but rather that because of host resistance and/or tumor cell properties, disseminated cells are incapable of growth elsewhere in the body. Thus, the improved survival observed in patients with negative lymph nodes may be a reflection of a tumor-host relationship which inhibits the growth-disseminated tumor cells.[22]

When one reviews the larger series of patients treated with these various methods of therapy, it is surprising to note the similarity of results. In almost all instances, regardless of the treatment employed, the 5 year cure rate for Stage 1 carcinoma of the breast is between 70 and 85 per cent. For Stage 2 carcinoma, the 5 year survival rate varies between 50 and 70 per cent. These survival rates have been interpreted by some as evidence that less extensive procedures are equally effective in treating carcinoma of the breast. However, several objections can be made to such inferences.

Most of these studies are nonrandomized and are not prospective. Prospective randomization of patients is essential, for only in this manner can such variables as age, menstrual status, location of tumor, duration of the presence of tumor, size of tumor, and pathologic cell type be eliminated. Only when both the control group and the study group have large numbers of patients in each of these categories can adequate comparisons be made.

Frequently, survival statistics are quoted from studies in which the patients have not been staged at all or have been staged by the author's own nonstandardized systems. When this occurs, it is impossible to tell whether the authors were highly selective in choosing only those patients who had a favorable prognosis for their procedure. Since accurate universally accepted standards of staging are now available, it is totally unacceptable for any author to present a series of cases which have not been staged according to accepted criteria.

When lumpectomy is used as a treatment for primary breast cancer, the problem of multicentricity of the tumor must be considered. In 1969, Gallagher and Marten,[23] studying 38 whole breast specimens, found that three fourths of the patients had other areas of the breast which were involved with either intraductal carcinoma, cellular hyperplasia, or epithelial atypism, and at least 50 per cent of these breasts had other sites of invasive carcinoma. They concluded, "all branches of a single nipple duct may be involved and this may be segmental or discontinuous."

Shah and associates[24] in 1973 found that 59 per cent of 508 patients who had an excisional biopsy of a malignant tumor prior to mastectomy still had carcinoma present in the mastectomy specimen. Studies such as this have made surgeons skeptical of any treatment which does not remove all of the involved breast.

Many studies show a surprisingly nonuniformity of treatment. Some of the patients have preoperative x-ray, others have postoperative x-ray; some patients have simple mastectomy with occasional enlarged nodes at the base of the axilla removed; some patients are treated with chemotherapy; others have undergone hormonal manipulations. In order for these studies to be adequately evaluated, the treatment must be standardized in every patient.

At the present time, we can say with certainty that those women in whom carcinoma of the breast is confined to the breast have a much better chance of survival than those women in whom tumor is found in the regional lymph nodes. The evidence for this is incontrovertible. However, several extremely important questions remained unanswered: (1) Does removal of the regional lymphatics improve survival when the tumor is clinically confined to the breast? (2) Does removal of the regional lymphatics improve survival when those lymphatics have been invaded by tumor? (3) If destruction of the regional lymphatics does improve survival, is x-ray therapy as effective as surgical removal?

The national surgical adjuvant breast project, Protocol No. 4, is designed to answer these questions. Patients with Stage 1 carcinoma clinically confined to the breast have been randomized into radical mastectomy, simple mastectomy alone, and simple mastectomy with irradiation. Patients with clinical Stage 2 carcinoma clinically involving the axillary lymph nodes are divided into radical mastectomy and simple mastectomy plus radiation therapy. Once large numbers of patients in each of these groups have been adequately studied for 10 years, hopefully, we will have the answers to these important unanswered questions.

At the present time, what is the best advice a surgeon can give to his patients? With our current state of knowledge, removal of the breast and the axillary contents appears to be the safest mode of therapy.

Other less radical procedures have never been shown to improve the survival rate. Whereas, some patients may do as well with lesser procedures, we are still unable to accurately identify these patients. The surgeon must merely exercise an educated guess as to which patients may be treated as successfully with a less radical procedure. Such a guess, even though it be an educated guess, subjects the patient to undue risk and is not warranted.

Though the name of Halsted has become synonymous with radical mastectomy, perhaps the statement with which he began his 1907 paper will ultimately prove to be his most valuable contribution: "It is especially true of breast cancer that the surgeon interested in furnishing statistics may in perfectly honorable ways provide them. The most conscientious man may refuse to operate upon any but favorable cases, and by performing an incomplete operation, exclude from his list of complete operations such bad ones as he finds himself operating upon."

This is an admonition to all of us to remain skeptical, to challenge new modes of therapy, to refuse to accept theory for fact, and to design experimental and clinical studies which scientifically test new hypotheses. Only in this manner will changes in the management of breast carcinoma be based less on emotion and more on reason.

REFERENCES

1. Halsted, W. S.: The treatment of wounds with especial reference to the value of the blood clot in the management of dead spaces, Johns Hopkins Hosp. Rep. **2:** 255, 1890-91.
2. Handley, W. S.: Cancer of the breast and its operative treatment, London, 1907, W. Sampson.
3. Halsted, W. S.: The results of radical operations for the cure of carcinoma of the breast, Ann. Surg. **46:** 1, 1907.
4. Haagensen, C. D., and Stout, A. P.: Carcinoma of the breast. II. Criteria operability, Ann. Surg. **118:** 859, 1032, 1943.
5. Haagensen, C. D., and O'Beid, S. G.: Biopsy of the apex of the axilla in carcinoma of the breast, Ann. Surg. **149:** 149, 1959.
6. Haagensen, C. D., and Cooley, E.: Radical mastectomy for mammary carcinoma, Ann. Surg. **170:** 884, 1969.
7. Wangensteen, O. H.: Superradical operation for breast cancer in the patient with lymph node involvement, Proc. Natl. Cancer Conf. **2:** 230, 1952.
8. Kaae, S., and Johansen, H.: Breast cancer; Five year results, Am. J. Roentgenol. **87:** 82, 1962.
9. Dahl-Iversen, E., and Tobiassen, T.: Radical mastectomy with parasternal and supraclavicular dissection for mammary carcinoma, Ann Surg. **157:** 170, 1963.
10. Urban, J. A.: What is the rationale for an extended radical procedure in early cases? J. A. M. A. **199:** 742, 1967.
11. Patey, D. H., and Dyson, W. H.: The prognosis of carcinoma of the breast in relation to the type of operation performed, Br. J. Cancer **2:** 7, 1948.
12. Gray, H. J.: Relation of the lymphatic vessels to the spread of cancer, Br. J. Surg. **26:** 462, 1939.
13. Auchincloss, H.: Significance of location and number of axillary metastases in carcinoma of the breast: A justification for a conservative operation, Ann. Surg. **158:** 37, 1963.
14. McWhirter, R.: The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast, Br. J. Radiol. **21:** 599, 1948.
15. Williams, J. G., Murley, R. S., and Curven, M. P.: Carcinoma of the female breast: Conservative radical surgery, Br. Med. J. **2:** 787, 1953.
16. Kaae, S., and Johansen, H.: Simple mastectomy plus postoperative irradiation by the method of McWhirter for mammary carcinoma, Prog. Clin. Cancer **1:** 453, 1965.
17. Brinkly, D., and Haybittle, J. L.: Treatment of stage II carcinoma of the female breast, Lancet **2:** 291, 1966.
18. Adair, F. E.: The role of surgery and irradiation in cancer of the breast, J.A.M.A. **121:** 553, 1943.
19. Mustakallio, S.: Treatment of breast cancer by tumor extirpation and roentgen therapy instead of radical operation, J. Fac. Radiol. **6:** 23, 1954.
20. Crile, G. Esselstyn, C. B., Herman, R. E., and Hoerr, S. O.: Partial mastectomy for carcinoma of the breast, Surg. Gynecol. Obstet. **136:** 929, 1973.
21. Handley, R. S.: The early spread of breast carcinoma and its bearing on operative treatment, Br. J. Surg. **51:** 206, 1964.
22. Fisher, B.: The surgical dilemma in the primary therapy of invasive breast cancer: A critical appraisal, Curr. Probl. Surg. Oct. 1970.
23. Gallagher, H. S., and Marten, J. E.: The study of mammary carcinoma by mammography and whole organ sectioning, Cancer **23:** 855, 1969.
24. Shah, J. P., Rosen, P. O., and Robbins, G. F.: Pitfalls of local excision in the treatment of carcinoma of the breast, Surg. Gynecol. Obstet. **136:** 721, 1973.

Decreasing postpartum sexual abstinence time

A. CULLEN RICHARDSON, M.D.
JAMES B. LYON, M.D.
ETHEL E. GRAHAM, R.N.
NANCY L. WILLIAMS, B.S., R.N.
Atlanta, Georgia

Postpartum sexual abstinence time can be safely shortened for most patients when episiotomy repair is done meticulously with fine PGA suture on small needles. The time preferred by patients for resumption of intercourse seems to be between the second and third postpartum week. We have seen no ill effects from this, and we feel that sexual intercourse at these early dates does not influence the healing of the episiotomy in any way.

THE PERIOD immediately following the birth of a child is one of physical and emotional adjustment for both parents. An ideal expression of the love and tenderness they feel for each other might be found in mutually satisfying sexual intercourse. Enforced abstinence, however, is the usual rule during the 6 weeks immediately following birth. We believe that this period can be shortened safely so that the husband and wife need not be kept apart sexually for so long a time.

Since 1971, our postpartum instructions given to all patients simply states, "You may resume intercourse any time you so desire after the bleeding slows."

Method

We recently reviewed the records of over 800 consecutive vaginal deliveries with episiotomies during the years 1972 through 1974. Median episiotomies were used routinely. In 6 per cent of the patients the incision was either made through the rectum or extended into the rectum. Over 98 per cent returned for postpartum examination. We found that a majority of patients were beginning regular coitus reasonably comfortably between postpartum days 14 and 21 (the earliest being day 5 and a few waiting until after the first postpartum examination at 4 weeks). We found no evidence to indicate that the early resumption of sexual activity adversely affected healing of the perineum in any way. All episiotomies healed primarily. There were no breakdowns or fistulas, and the anatomic result was uniformly satisfactory.

Obviously, this voluntary early resumption of intercourse attests to a lack of excessive perineal soreness and pain. This we attribute to two things: meticulous surgical technique and the use of fine suture material that excites a minimal tissue reaction.

An attempt was made to carefully approximate each anatomic layer in the perineum with multiple small sutures on very fine needles. No stitch was taken more than 3 mm. deep to the edge of the incision. The resultant wedge of tissue along the incision that had sustained the trauma of needle puncture and contained any foreign material was limited to about 5 mm. in thickness. No attempt was made to close dead space; rather, each fascial and muscle layer was carefully identified and approximated without tying sutures tightly.

All repairs were done with polyglycolic acid PGA suture. A 4-0 suture swedged onto a T-5 (gastrointestinal) needle and a 5-0 suture on a T-16 needle were both used in these patients with equal success. All authors prefer the 5-0 with the T-16 needle, as this very small needle and suture lend themselves to a more meticulous repair. The opinion that fine suture will cut through the perineal tissue has not been substantiated in our experience.

Before 1971, we sutured all episiotomies with 4-0 chromic gut and found that patients experienced some perineal pain. With a change to PGA sutures in 1971, we saw a noticeable decrease in tenderness and induration in the perineal area.

We did not quantitate pain on our patients, but floor nurses noted that very few patients sutured with PGA required medication for perineal pain. The time of the postpartum examination has been changed from the traditional 6 weeks to 4 weeks. The minimal perineal induration and tenderness at this examination has been striking since the switch to PGA suture.

Reprint requests: Dr. A. C. Richardson, 710 Peachtree St., N. E., Atlanta, Georgia 30308.

Results

Our subjective observation of less postepisiotomy pain when PGA sutures are used has been confirmed by others.[1, 2] Livingstone, Simpson, and Naismith[1] reported a significant reduction in the degree of pain in patients repaired with PGA as compared to those repaired with catgut. Rogers[2] investigated postepisiotomy pain in 301 patients sutured with chromic catgut and 299 sutured with PGA sutures. When his evaluations of incidence and degree of pain were analyzed statistically, the results showed that the over-all pain and the stitch pain experienced with PGA were about half of the pain experienced with chromic catgut sutures. Our observations are also in agreement with those of Tompkins and Lea,[3] whose obstetric patients sutured with PGA complained less and appeared more comfortable during the first postpartum week.

Several researchers have reported postpartum perineal pain as one of the factors influencing early resumption of intercourse.[3, 5] Falicov[4] stated that, despite high levels of desire, seven of the 19 women in her study group delayed sexual activity for fear of soreness caused by episiotomy. Two couples resumed sexual activity 4 weeks after delivery, and 10 began between 6 and 7 weeks post partum. Six women reported that tension, fatigue, or physical discomfort caused by engorgement of the breasts or soreness of the episiotomy site interfered with their reaching their prepregnancy level of sexual interaction.

Masters and Johnson[5] found similar reasons expressed by 101 women viewed 3 months post partum. They reported that, aside from concern for the possibly injurious effects of too rapid return to coital activity, 54 women said that the only real deterrents to early sexual activity were perineal pain or vaginal-barrel irritation.

A detailed, controlled investigation of the relationship between the time of resumption of coitus and the reduction of perineal pain through careful surgical technique and choice of suture material would seem to be the next step.

We hear much today about techniques and systems of childbirth designed to enhance the interpersonal interaction between husband and wife and deepen the marriage relationship. The sacredness and joy of human reproduction has been examined.[6] Certainly we as obstetricians cannot insure marital bliss. However, the early resumption of comfortable coitus during this period of intense emotion can only be a plus for any marriage.

On the basis of our clinical experience, we believe that postpartum sexual abstinence time can be safely shortened for most patients when episistomy repair is done meticulously with fine PGA suture on small needles. The time preferred by patients for resumption of intercourse seems to be between the second and third postpartum weeks. We have seen no ill effects from this, and we feel that sexual intercourse at these early dates does not influence the healing of the episiotomy in any way.

REFERENCES

1. Livingstone, E., Simpson, D., and Naismith, W. C. M. K.: A comparison between catgut and polyglycolic acid sutures in episiotomy repair, J. Obstet. Gynaecol. Br. Commonw. **81:** 245 1974.
2. Rogers, R. E.: Evaluation of post-episiorrhaphy pain: Polyglycolic acid vs catgut sutures, Milit. Med. **139:** 102, 1974.
3. Tompkins, M. G., and Lea, R. H.: The use of polyglycolic acid sutures in obstetrics and gynecology, Can. Med. Assoc. J. **106:** 675, 1972.
4. Falicov, C. J.: Sexual adjustment during first pregnancy and postpartum, Am. J. Obstet. Gynecol. **117:** 991, 1973.
5. Masters, W. H., and Johnson, V. E.: Human Sexual Response, Boston, 1966, Little, Brown & Company, pp. 161-163.
6. Richardson, A. C., and Webber, L. D.: The noetic dimension of human reproduction, Am. J. Obstet. Gynecol. **110:** 808, 1971.

GYNECOLOGY

Abnormal cervical cytology in the teen-ager: A continuing problem

MARTIN J. FELDMAN, M.D.
E. MICHAEL LINZEY, M.D.
ELENA SREBNIK, B.A.
DERYCK R. KENT, M.D.
ARTHUR I. GOLDSTEIN, M.D.
MORTON NELSON, M.D., M.P.H.
Irvine, California

Abnormal cervical cytology is being discovered in an alarming number of sexually active teen-agers. Over an 18 month period, cytology consistent with mild dysplasia or worse was noted in 188 of 2,655 teen-agers screened. This represents a rate of 70.8 per thousand. Colposcopically directed biopsies in 65 patients revealed 15 cases of severe dysplasia–carcinoma in situ. Cryosurgery was the principle method of treatment and, combined with colposcopy, is a safe and effective means of managing these patients.

OVER THE PAST FIFTEEN years, only a minimal number of studies[1–3] have specifically discussed cervical cytology in the teen-ager. Written primarily to justify routine screening, they have called attention to the presence of abnormal cytology and histology in a substantial number of women between the ages of 13 and 19. Since invasive carcinoma in the teen-ager is extremely rare, the real significance of this problem lies in the future potential of intraepithelial lesions. If cervical carcinoma is indeed a preventable disease, careful evaluation and management must start with these young women.

The purpose of this paper is to present our experience with abnormal cervical cytology in teen-agers, discuss its importance, and recommend a program of outpatient evaluation and management.

From the Departments of Gynecology and Obstetrics, Pathology, and Family Medicine, University of California at Irvine.

Received for publication April 2, 1976.

Accepted May 19, 1976.

Reprint requests: Dr. Martin J. Feldman, University of California, Irvine, College of Medicine, Department of Obstetrics and Gynecology, Irvine, California 92717.

Material and methods

During an 18 month period beginning in July of 1974, the cytology laboratory at Orange County Medical Center screened a total of 2,655 Papanicolaou smears from women between the ages of 13 and 19. This represents 20.7 per cent of the total patients screened during the same period. The majority of these teen-agers were white and in the low-income segment of the population. The cytology was reported as normal (2,316) or consistent with inflammation (151) in 2,467 cases. The remaining 188 patients (7 per cent) had abnormal cytology consistent with mild dysplasia or worse. The age and cytology of these 188 patients are shown in Table I.

Patients with abnormal Papanicolaou smears were strongly encouraged to be seen in the Special Papanicolaou Clinic where colposcopy and colposcopi-

Table I. Relationship of age to abnormal cytology

Age of patient (yr.)	*Cytology*				*No. of patients screened*
	Mild dysplasia	*Moderate dysplasia*	*Severe Dysplasia*	*Carcinoma in situ*	
13	1	0	0	0	17
14	0	0	0	0	42
15	3	2	0	0	148
16	6	4	1	0	302
17	16	7	2	0	500
18	47	22	1	1	736
19	44	21	10	0	910
Total	117	56	14	1	2,655

Table II. Comparison of cytologic diagnosis with results of directed biopsy

Cytology	*Biopsy*				
	Mild dysplasia	*Moderate dysplasia*	*Severe dysplasia*	*Carcinoma in situ*	**Other*
Mild dysplasia	13	4	2	0	10
Moderate dysplasia	3	10	6	0	4
Severe dysplasia	2	3	3	3	1
Carcinoma in situ	0	0	0	1	0

*Chronic cervicitis, metaplasia, etc.

Table III. Patient management

Diagnosis	*Treatment*		
	Conization	*Cryosurgery*	**Other*
Mild dysplasia	0	8	3
Moderate dysplasia	0	11	0
Severe dysplasia	4	7	0
Carcinoma in situ	0	4	0
Chronic cervicitis	0	3	10

*Follow-up, medication, etc.

cally directed biopsies are the primary means of evaluation. Despite all efforts, only 65 patients were evaluated. Subsequent management was based on the results of colposcopy and biopsy. For an intraepithelial lesion, the possibilities included follow-up only, medication, cryosurgery with nitrous oxide used as the refrigerant, and cervical conization. In the use of cryosurgery, many of the principles and techniques of Townsend[1] were adopted. Full visualization of the entire transformation zone was and is an absolute prerequisite for cryosurgery.

Results

All 65 teen-agers seen in the Special Papanicolaou Clinic were sexually active. Thirty-six patients (55 per cent) had been pregnant one or more times. There was no relationship between parity and the degree of cytologic atypia.

Cytology and the results of colposcopically directed biopsies are compared in Table II. In every case the entire transformation zone could be seen and the examination was considered satisfactory. It should be noted that there were false positive as well as false negative cytology reports. In two cases, mild dysplasia was the lesion predicted, but directed biopsy revealed severe dysplasia. After thoroughly reviewing the Papanicolaou smears, we attributed this to sampling error. On the other hand, in three cases where the cytology was consistent with severe dysplasia, examination and biopsy revealed mild dysplasia in two patients and chronic cervicitis in a third. Repeat cytology and colposcopy confirmed the false positive interpretation of the original smear. Chronic cervicitis was the only lesion present in 15 cases. None of the patients had invasive carcinoma.

The management of these teen-agers is shown in Table III. Fifteen patients did not return for treatment. The four cervical conizations were performed very early in the study when we were primarily interested in evaluating the accuracy of our colposcopically directed biopsies. No teen-ager has had a cervical conization since that time.

It can be seen that cryosurgery was the primary method of treatment for all grades of intraepithelial neoplasia. Following cryosurgery, patients are seen every three months for repeat cytology. After three negative smears, the interval is lengthened to six months. Although the number of patients is small and

the follow-up in many cases is less than a year, we have had no complications or recurrences thus far.

Comment

Ferguson[1] was the first to call attention to the teen-ager with abnormal cytology. He noted 66 Class III and 11 Class IV smears in approximately 2,300 teen-agers screened, for a rate of 33.5 per thousand. Subsequent tissue diagnosis with the use of punch biopsy and/or cervical conization revealed 10 cases of carcinoma in situ and 20 cases of dysplasia. He concluded that ". . . younger patients should not be denied a cancer smear during a routine pelvic examination." This conclusion was supported by Kaufman and associates[2] who reported 296 "inconclusive," and six positive smears for carcinoma in situ of 10,246 teenagers screened, a rate of 29.5 per thousand. Tissue was obtained in 49 patients and revealed 15 cases of severe dysplasia–carcinoma in situ and 23 cases of mild to moderate dysplasia.

In the present study, 70.8 smears per thousand teen-agers screened had cells consistent with mild dysplasia or worse, a higher figure than previously reported. Colposcopically directed biopsies demonstrated some degree of intraepithelial neoplasia in 50 of 65 cases, for a rate of 18.8 per thousand screened. If one only considers the 15 cases of biopsy-proved severe dysplasia–carcinoma in situ, the rate is 5.6 per thousand screened. Although these figures are significant by themselves, they would have been higher had all 188 teen-agers undergone colposcopic evaluation.

Because of the extremely small number of invasive carcinomas discovered, the validity of extensive screening programs in young women recently has been questioned.[5] We do not agree with this line of reasoning. The detection of intraepithelial neoplasia is important and clearly justifies the time and expense involved in routine screening. Many of these lesions will progress, and a few may ultimately lead to invasive carcinoma, a concept supported by statistical data[6, 7] and prospective studies.[8–10] Stern,[7] for example, noted that the incidence of carcinoma in situ was 49 per thousand in patients with a previous diagnosis of dysplasia as opposed to 0.04 per thousand without dysplasia. For invasive carcinoma, she found an incidence of 4.0 and 0.04 per thousand in a population with and without dysplasia.

Patients studied in previous reports as well as our own have been from sexually active clinic populations. That this represents a high-risk group has been confirmed by numerous epidemiologic studies[11] associating early onset of sexual intercourse with cancer of the cervix. Whether the so-called "teen-age sexual revolution" will significantly extend this problem to the private practitioner remains to be seen. However, early and frequent sexual intercourse with multiple partners is no longer primarily limited to any one social strata of our society. Regular screening is strongly recommended regardless of socioeconomic status.

Colposcopy, a clinical method of proved accuracy,[12, 13] is an excellent means of evaluating the teen-ager with abnormal cytology. It avoids the expense, psychological pressures, and potential short- and long-term morbidity of diagnostic cervical conization. In addition, cytology is subject to occasional false positive interpretations[14] which may result in an unnecessary conization. A report by Wallace and Slankard[3] revealed that seven of 51 cervical conizations in teen-agers with two consecutive suspicious smears or one positive smear failed to demonstrate any pathology. In 32 cases, dysplasia of an undefined degree was discovered. In the present series, three patients had false positive smears. Before the era of colposcopy at our institution, cone biopsies would have been performed.

With the availability of colposcopy, it no longer seems justified to follow clinic patients with cytologic evidence of mild or moderate dysplasia, with the hope that the next smear will be normal and with evaluation planned only if an abnormality persists or progresses. In the very young, totally asymptomatic woman, delay often results in losing the patient to follow-up. In addition, past experience has shown that approximately 20 per cent of these patients will have significantly more advanced lesions.[13]

Our current policy is to manage all teen-agers with intraepithelial neoplasia and satisfactory colposcopy on an outpatient basis with the use of cryosurgery. A second colposcopic examination is performed immediately prior to treatment to reaffirm the distribution of the lesion and ensure adequate coverage by the freeze ball. The procedure is well tolerated by this group of patients and is an excellent alternative to hospitalization and conization. Townsend[4] and others[15, 16] have shown the results of cryosurgery to be as good as or better than those obtained with cervical conization with far fewer complications.

In conclusion, abnormal cervical cytology has been found in a substantial number of sexually active women between the ages of 13 and 19. Continued close cytologic surveillance of this age group is recommended. Although one must always consider the possibility of invasive carcinoma, in almost every case an abnormal smear will indicate an intraepithelial lesion. Colposcopy and cryosurgery offer an effective means of evaluating and treating these young women on an outpatient basis.

REFERENCES

1. Ferguson, J. H.: Positive cancer smears in teenage girls, J. A. M. A. **178:** 365, 1961.
2. Kaufman, R. H., Burmeister, R. E., and Spjut, H. J.: Cervical cytology in the teen-age patient, AM. J. OBSTET. GYNECOL. **108:** 515, 1970.
3. Wallace, D. L., and Slankard, J. E.: Teenage cervical carcinoma in situ, Obstet. Gynecol. **41:** 697, 1973.
4. Townsend, D. E.: Cryosurgery in gynecology, *in* Taymor, M. L., and Green, T. H., Jr., editors: Progress in Gynecology, New York, 1975, vol. 6, Grune & Stratton, Inc., pp. 583-595.
5. Massachusetts Department of Public Health: Papanicolaou testing—are we screening the wrong women? N. Engl. J. Med. **294:** 223, 1976.
6. Johnson, L. D., Nickerson, R. J., Easterday, C. L., Stuart, R. S., and Hertig, A. T.: Epidemiological evidence for the spectrum of change from dysplasia through carcinoma in situ to invasive cancer; Cancer **22:** 901, 1968.
7. Stern, E.: Epidemiology of dysplasia, Obstet. Gynecol. Survey **24:** 711, 1969.
8. Fox, C. H.: Biologic behavior of dysplasia and carcinoma in situ, AM. J. OBSTET. GYNECOL. **99:** 960, 1967.
9. Richart, R. M., and Barron, B. A.: A follow-up study of patients with cervical dysplasia, AM. J. OBSTET. GYNECOL. **105:** 386, 1969.
10. Sedlis, A., Cohen, A., and Sall, S.: The fate of cervical dysplasia, AM. J. OBSTET. GYNECOL. **107:** 1065, 1970.
11. Rotkin, I. D.: A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents, Cancer Res. **33:** 1353, 1973.
12. Stafl, A., and Mattingly, R. F.: Colposcopic diagnosis of cervical neoplasia, Obstet. Gynecol. **41:** 168, 1973.
13. Feldman, M. J., Kent, D. R., Linzey, E. M., and Goldstein, A. I.: The making of a colposcopist—A safe and sensible approach, J. Reprod. Med. **16:** 73, 1976.
14. Seybolt, J. E., and Johnson, W. D.: Cervical cytodiagnostic problems—A survey, AM. J. OBSTET. GYNECOL. **109:** 1089, 1971.
15. Crisp, W. E.: Cryosurgical Treatment of neoplasia of the uterine cervix, Obstet. Gynecol. **39:** 495, 1972.
16. Kaufman, R. H., Thomas, S., Norton, P. K., and Conner, J. S.: Cryosurgical treatment of cervical intraepithelial neoplasia, Obstet. Gynecol. **42:** 881, 1973.

Virucidal effect of certain chemical contraceptives on Type 2 herpesvirus

BALWANT SINGH, PH.D.
BOSKO POSTIC, M.D.
JOHN C. CUTLER, M.D.
Pittsburgh, Pennsylvania

The virucidal effect of several chemical contraceptives was investigated and the findings are reported. The suspension of Type 2 herpes simplex virus, containing 10^6 to 10^7 tissue culture infectious doses per 0.1 ml., was inactivated on exposure to five different chemical contraceptives. For quantitative estimates of virucidal effect, 10 per cent solutions of these chemical contraceptives were tested with an exposure time of 10 minutes at room temperature. The methods for determination of residual infectivity included both virus assays in cultures of Vero cells and human embryo fibroblasts, as well as the intracranial inoculation of mice. Virus infectivity decreased 1,000- to 10,000-fold after contact with chemical contraceptives, indicating a substantial virucidal effect.

THE REPORTED CASES of gonorrhea in the United States have tripled during the last 15 years, and it is believed that they represent only a fraction of the total cases which occur in this country. There has also been a concurrent rise in the incidence of several other genital infections caused by various pathogens including herpesvirus, cytomegalovirus, Chlamydia, Mycoplasma, and Trichomonas. Frequently, two or more of these agents are recovered simultaneously from patients attending venereal disease clinics.[1] Various nongonococcal genital infections are found much more often among sexually active younger women. In England, where statistics are available on the incidence of nongonococcal genitourinary infections, nonspecific urethritis in men is now more frequent than gonorrhea.[2]

Public health has long been concerned with the control of syphilis and gonorrhea as venereal disease, but has given little attention to other genital infections, such as herpes genitalis which was recognized and described as a venereal disease as early as 1885.[3] The incidence of herpes genitalis is far greater than generally realized. The majority of patients with primary herpes infections are teen-age girls and unmarried women. Seventy per cent or more of infected women may have no symptoms.[4] In the female subject, the cervix appears to be the chief site of infection and when the disease is limited to the cervix there may be little or no symptomatology.[4] Male subjects may also harbor the virus asymptomatically which can be isolated from the male urethra as well as from the semen.[4, 5] This asymptomatic carriage of the virus by members of both sexes contributes significantly to spread of the disease. During the last ten years, considerable literature has accumulated suggesting an association of Type 2 herpes simplex virus infections of the genital tract and the development of cervical cancer. Several studies have also shown a significant association of genital herpes with other venereal infections, indicating its importance in venereal disease control programs. In view of the growing concern with increasing frequencies of sexually transmitted diseases, as well as unplanned pregnancies, a research project was undertaken at the University of Pittsburgh to identify vaginal contraceptive preparations with a potential for topical prophylaxis against genital infections. Various types of chemical contraceptives, creams, foams, jellies, vaginal suppositories, and foaming tablets marketed in the United States and other countries for intravaginal use

From the Graduate School of Public Health, University of Pittsburgh.

Supported in part with funds from the Agency for International Development under Contract A.I.D./csd-2822.

Received for publication April 29, 1976.

Accepted June 18, 1976.

Reprint requests: Dr. Balwant Singh, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261.

Table I. Titration of Type 2 herpesvirus in tissue culture before and after treatment with chemical contraceptives

Contraceptive tested	*Assay system*	*Virus titration* (log $TCID_{50}$/0.1 ml.)*	
		Before	*After*
Conceptrol	Vero cell	6.0	≤2.5
Cooper creme	Vero cell	6.0	≤2.5
Conceptrol	HEF	6.5	≤3.5
Cooper creme	HEF	6.5	≤3.5

*Virus suspension was mixed with an equal volume of contraceptive (10 per cent solution) and after 10 minutes serial dilutions were inoculated in Vero cells from 10^{-3} to 10^{-8} and HEF from 10^{-4} to 10^{-9}. $TCID_{50}$ was calculated by the Reed-Muench[9] method.

Table II. Titration of Type 2 herpesvirus in mice before and after treatment with chemical contraceptives

Contraceptive tested	*Intracerebral log LD^{50}/0.03 ml.**	
	Before	*After*
Preceptin gel	5.3	≤0.5
Conceptrol	5.3	≤1.5
Cooper creme	5.3	≤2.5
Lorophyn jelly	5.3	1.7
Milex crescent jelly	5.3	≥4.5

*LD^{50} titers were calculated by the Reed-Muench[9] method. Virus suspension was mixed with an equal volume of contraceptive (10 per cent solution), and after 10 minutes' exposure serial dilutions were injected intracerebrally, 0.03 ml. per mouse and 12 mice per dilution.

were studied in vitro for their antimicrobial effects on *Treponema pallidum, Neisseria gonorrhoeae, Trichomonas vaginalis,* and *Candida albicans* as reported previously.[6, 7] The virucidal effect of selected contraceptives on Type 2 herpesvirus was also determined, and the relevant findings are presented in this paper.

Material and methods

Virus strain. Type 2 herpesvirus (196-P10, of October 8, 1970) was obtained from Dr. William E. Rawls (Department of Virology and Epidemiology, Baylor University College of Medicine, Houston, Texas). One additional passage was made in human embryonic fibroblast (HEF) cell culture in our laboratory. After 48 hours of incubation, the virus harvest was prepared, and ampules containing the infectious suspension were stored at about −65° C. This stock contained $10^{6.5}$ tissue culture infectious doses ($TCID_{50}$) per 0.1 ml.

Virus assay. The $TCID_{50}$ of virus was determined in human embryonic fibroblasts (HEF) and Vero cells. The human cell culture was prepared from a locally derived cell strain.[8] The HEF were grown in medium consisting of Hanks balanced salt solution (HBSS) supplemented with 0.5 per cent lactalbumin hydrolyzate 2 mM. L-glutamine, Eagle's vitamin mixture, antibiotics, and 5 per cent inactivated (56° C. for 30 minutes) newborn calf serum. The medium for Vero cells (African Green Monkey kidney cell line) was Eagle's basal medium supplemented with 5 per cent inactivated newborn calf serum, sodium bicarbonate, and antibiotics. Tubes with confluent monolayers were used in these experiments. The stock virus suspension was serially diluted tenfold, with the specific cell culture medium or physiologic saline solution used as diluent. Four cell culture tubes were inoculated from each of the serial virus dilutions with 0.1 ml. of inoculum per tube. The inoculated tissue culture tubes were incubated at 37° C., and the end points of infectivity were determined by reading the cytopathogenic effect (CPE).

The intracerebral 50 per cent lethal dose (LD_{50}) of virus for mice was determined by injecting 0.03 ml. per weaning mouse in twelve mice for each serial virus dilution. Pathogen-free albino Swiss mice* seven to eight weeks old were used in all experiments. Injected mice were observed for 21 days for typical illness and death.

The infectivity and lethal virus dose were calculated by the method of Reed and Muench.[9]

Virucidal procedures. The chemical contraceptives tested for their virucidal effects were over-the-counter products purchased locally. Initial 10 per cent (weight/volume) working solutions of contraceptives and subsequent tenfold dilutions (volume/volume) were prepared in physiologic saline solution. For preliminary experiments, two or more virus dilutions were mixed with one or more dilutions of contraceptive solutions, but, for quantitative estimates of virucidal effect, an aliquot of ten per cent working solution of respective contraceptive was mixed with an equal volume of the high-titer virus suspension. After 10 minutes of incubation at room temperature (23° C.), serial tenfold dilutions from virus-contraceptive mixture were prepared rapidly, and the residual infectivity was titered in cell culture tubes or by intracerebral mice inoculation.

In each experiment, the virus was also quantitated without contraceptive treatment, and uninfected controls were included for serial dilutions of contraceptive solution and diluents. This served to monitor for the toxicity of these compounds for cultured cells or animals used in virus assays.

*Charles River Breeding Labs., Inc., Hazelton, Massachusetts.

Results

The effect of virus treatment with 10 per cent solutions of two different chemical contraceptives in shown in Table I. The infectivity titration of virus without treatment was $10^{6.0}$ and $10^{6.5}$ per 0.1 ml. in Vero cells and HEF, respectively. After treatment with these contraceptives, the virus was inactivated, and the virucidal effect of these preparations is based on this evidence. No cytopathic effect was seen in Vero and HEF cell culture tubes inoculated with contraceptive-treated virus suspensions diluted with 10^{-3} to 10^{-8} and 10^{-4} to 10^{-9} virus, respectively. The cell culture tubes inoculated with varying concentrations of contraceptive solution alone showed chemical toxicity up to dilutions of 10^{-2} for Vero cells and 10^{-3} for HEF cell cultures, respectively. When the chemical toxicity of contraceptives is considered, the $TCID_{50}$ per 0.1 ml. of residual virus after treatment was estimated to be ≤ 2.5 logs in Vero cells and ≤ 3.5 logs for HEF cell culture tubes (Table I).

The results of virus assay in weanling mice both with and without treatment are shown in Table II. The intracerebral LD_{50} per 0.03 ml. of virus prior to treatment was 5.3 but considerably less after treatment with 10 per cent solutions of various chemical contraceptives. The 50 per cent lethal dose of residual virus after treatment with contraceptives (Conceptrol, Cooper creme, Preceptin gel, Lorphyn jelly, and Milex crescent jelly) ranged from <0.5 to >4.5 logs. Mice in control groups injected with serial dilutions of various contraceptive solutions alone (0.03 ml. per mouse) died after inoculation with the 10^{-1} dilution, except for those inoculated with Milex crescent jelly which was lethal in all dilutions from 10^{-1} to 10^{-4}. The death patterns due to acute toxicity of contraceptive and virus infection were quite different. The major proportion of deaths due to contraceptives occurred within 26 to 48 hours whereas deaths due to herpesvirus were noted after five days.

Comment

The virucidal effects of several chemical contraceptives investigated are reported in this study. Both tissue culture techniques and the mouse inoculation method were used for the quantitation of residual viral infectivity. It was observed that Type 2 herpes simplex virus containing the original infectious suspension of 6 to 7 logs ($TCID_{50}$ per 0.1 ml.) was inactivated upon contact with several chemical contraceptives, even when 10 per cent solutions of these contraceptives were used. Tissue culture tubes of Vero cells and HEF inoculated with virus treated with 10 per cent solutions of the contraceptives tested did not show any cytopathic effect attributable to the residual infectious inoculum. It has been reported by other investigators that ether-sensitive viruses (the arboviruses, the herpes group, and the myxoviruses and related viruses) are inactivated by benzalkonium chloride and related quaternary ammonium germicides.[10] The virucidal effect of chemical contraceptives observed in this study is most likely due to quaternary and other surfactant compounds present in these products.

Three possible factors could interfere with the observation of a virucidal effect in assay systems. These are effects of serum proteins, pH, and temperature. However, their influence was minimized by appropriate experimental conditions and controls. Thus, the observed reduction in virus infectivity amounting to several logs[10] was not due to any factor other than the virucidal effect of chemical contraceptives.

To assure optimal conditions for the measurement of infectivity, the dilutions of virus before and after treatment with contraceptives were prepared in diluent containing 5 per cent inactivated calf serum. Irrespective of any stabilizer present in the diluent, the treatment with contraceptives was effective in inactivating the virus, and no cytopathic effect was observed in the inoculated cell culture tubes beyond that attributed to the toxicity of these contraceptives up to dilutions of 10^{-2} and 10^{-3} for both Vero cells and HEF, the latter being somewhat more vulnerable. Therefore, the virus assay for infectivity of residual virus after treatment was carried out by inoculating 10^{-3} to 10^{-8} in Vero cells and 10^{-4} to 10^{-9} dilutions in culture of HEF and the $TCID_{50}$ was calculated accordingly. Since the original suspension titered 10^{6} to 10^{7} of infectious virus per 0.1 ml., the 1,000- to 10,000-fold decrease in infectivity occurring after contact with chemical contraceptives indicates a substantial virucidal effect.

These experimental findings encourage further studies to determine the potential usefulness of chemical contraceptives in preventing sexually transmitted herpesvirus infection.

The authors wish to thank Mrs. Mary White for technical assistance.

REFERENCES

1. Wentworth, B. B., Bonin, P. A., Holmes, K. K., Gutman, L., Wiesner, P., and Alexander, E. R.: Isolation of viruses, bacteria and other organisms from venereal disease clinic patients: Methodology and products associated with multiple isolations, Health Lab. Sci. **10:** 75, 1973.

2. Willcox, R. R.: A world wide view of venereal disease, Br. J. Vener. Dis. **48:** 163, 1972.
3. Unna, P. G.: Herpes progenitalis especially in women, J. Cutan. Vener. Dis. **1:** 321, 1883.
4. Josey, W. E., Nahmias, A. J., and Nail, Z. M.: The epidemiology of Type 2 (genital) herpes simplex virus infection, Obstet. Gynecol. Survey **27:** 295, 1972.
5. Alexander, E. R.: Possible etiologies of cancer of the cervix other than herpes virus, Cancer Res. **33:** 1485, 1973.
6. Singh, B., Cutler, J. C., and Utidjian, H. M. D.: Studies on development of a vaginal preparation providing both prophylaxis against veneral disease, other genital infections and contraception. II. In vitro effect of contraceptive and non-contraceptive preparations on *Treponema pallidum* and *Neisseria gonorrhoeae,* Br. J. Vener. Dis. **48:** 57, 1972.
7. Singh, B., Cutler, J. C., and Utidjian, H. M. D.: In vitro effect of contraceptives and non-contraceptive preparations on *Candida albicans* and *Trichomonas vaginalis,* Contraception **5:** 402, 1972.
8. Ho, M., Tan, Y. H., and Armstrong, J. A.: Accentuation of production of human interferon by metabolic inhibitors, Proc. Soc. Exp. Biol. Med. **139:** 295, 1972.
9. Reed, L. J., and Muench, H. A.: Simple method of estimating 50% end points, Am. J. Hyg. **27:** 493, 1938.
10. Armstrong, J. A., and Froelich, E. J.: Inactivation of viruses by benzalkonium chloride, Appl. Microbiol. **12:** 132, 1964.

Induction of menstruation with bromocryptine in patients with euprolactinemic amenorrhea

GEORGE TOLIS, M.D.
FREDERICK NAFTOLIN, M.D., D.PHIL.
Montreal, Quebec, Canada

Three nulliparous women presented with secondary amenorrhea with no evidence of endocrinopathy and normal skull x-ray. Pulsatile gonadotropin secretion was reduced, but an adequate pituitary gonadotropin reserve was demonstrable with luteinizing hormone–release factor provocation. The administration of bromocryptine was associated with amplification of pulsatile secretion of gonadotropins and was followed, in two of the three, by ovulatory menstruation. It is suggested that bromocryptine should be considered for induction of menstruation in euprolactinemic secondary amenorrhea.

AMENORRHEA IN THE absence of pituitary tumor and associated with the presence of releasable pituitary gonadotropin has been defined as hypothalamic amenorrhea.[1,2] Induction of ovulation in patients with normal prolactin has been accomplished with the use of gonadotropin-releasing factor[3] or bromocryptine (2-bromo-α-ergocryptine) in the presence of high serum prolactin levels.[4, 5] The present report documents brococryptine-induced ovulation/menstruation in patients with euprolactinemic hypothalamic amenorrhea. This form of treatment may be of value in similar cases of euprolactinemic amenorrhea.

Case reports

Case 1. A 23-year-old medical student developed secondary amenorrhea at age 20 following a 25 pound voluntary weight loss while dieting. Menarche, at age 13, was followed by regular cycles. Treatment with thyroxine, 0.2 mg. daily for four months, had been without any effect. Equally ineffective were 2 five-day trials with clomiphene citrate, 100 mg. daily. At examination the patient had no emotional or other complaints. Positive findings included symmetrical vitiligo and a small uterus without palpable ovaries. She was 20 pounds underweight (according to Metropolitan Life tables); height was 5 feet and 6 inches, and weight was 110 pounds. No psychopathology was apparent. No milk could be expressed from the breasts. Hemogram, 12 parameter Sequential Multiple Analyzer test, and skull x-ray were normal. Serum thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) assessed from a single sample were 4.8 μg per 100 ml., 94 ng. per 100 ml., and 4 μU per milliliter, respectively. All were in the normal range (T_4, 4 to 11 μg per 100 ml.; T_3, 70 to 200 ng. per 100 ml.; TSH, 0 to 8 μU per milliliter).

The 24 hour urinary cortisol excretion was normal (56 μg per gram of creatinine). Basal serum concentrations of prolactin (PRL) follicle-stimulating hormone (FSH), and luteinizing hormone (LH)[2] were within normal limits by radioimmunoassay. Blood sampling every 20 minutes for three hours revealed maximum oscillations of 33 per cent for FSH and 60 per cent for LH (Fig. 1). at a time when basal serum estradiol (2.2 ng. per 100 ml.) was below the lowest level for the normal follicular phase range (4 to 12 ng. per 100 ml.) and progesterone was at follicular phase levels (0.1 ng. per milliliter). Following subcutaneous administration of 100 μg of LH-releasing factor (LRF),* a significant increase in both serum FSH and LH was noted (Fig. 2). Serum estradiol remained at preinjection levels during the two-hour observation period. The ratio of LH/FSH release favored LH; a prompt release of LH and FSH indicated a readily releasable pituitary gonadotropin pool.

Following these investigations, the patient was given bromocryptine,† 2.5 mg. by mouth twice daily and was

From the Departments of Medicine and Obstetrics and Gynecology, McGill University and The Royal Victoria Hospital.

Received for publication February 17, 1976.

Revised April 21, 1976.

Accepted April 26, 1976.

Reprint requests: Dr. George Tolis, Royal Victoria Hospital, 687 Pine Ave. W., Montreal, Quebec, Canada H3A 1A1.

*Luliberin, Ayerst Labs., Div. American Home Products Corp., 685 Third Ave., New York, New York, 10017.

†CB-154, Sandoz Pharmaceuticals, Div. of Sandoz-Wander, Inc., Route 10, Hanover, New Jersey 07936.

instructed to record the basal body temperature (BBT) daily. Fifty-three days later, when the BBT had been elevated by 1° F., the serum FSH, LH, and PRL secretion patterns were reassessed (Fig. 1, right panel). Serum PRL concentrations during the three-hour observation were consistently lower than pretreatment levels (mean pretreatment level 3.8 ng. per milliliter; mean level during treatment, 1.5 ng. per milliliter; $p < 0.005$). During this observation period, serum FSH and LH remained within normal ranges but exhibited oscillations greater than before treatment (109 per cent for FSH and 187 per cent for LH). On June 8, approximately 2 months from onset of the bromocryptine treatment, the patient menstruated for three days. The serum progesterone was > 8 ng. per milliliter on the day preceding menses (Fig. 3). Bromocryptine treatment was discontinued, and the patient has since been menstruating spontaneously.

Case 2. A 20-year-old nursing student presented with two years of secondary amenorrhea following the discontinuation of oral contraceptive medication* used for one year. Thyroxine treatment initiated for induction of menstruation had so far been unsuccessful. Height was 5 feet, 4 inches, and weight was 135 pounds (15 pounds overweight by Metropolitan Life tables). Physical examination was otherwise within normal limits. Skull x-ray was normal. Serum FSH, LH, and PRL were within normal limits (18 μg per 100 ml., 11 μg per 100 ml., and 8.4 ng. per milliliter, respectively.) Following the administration of 100 μg of LRF, serum FSH and LH reached peak levels of 125 and 94 μg per 100 ml., respectively, but no change was seen in serum estradiol, which remained at preinjection levels (2.6 ng. per 100 ml.). Clomiphene administration (200 mg. daily for seven days) induced an ovulatory LH peak and resulted in two days of vaginal bleeding. No further spontaneous bleeding was seen over the following six months. Bromocryptine administration, 2.5 mg. twice daily, resulted in three days of vaginal bleeding after 49 days. Spontaneous menstruation with a biphasic BBT was noted 30 days later.

Case 3. A 23-year-old unmarried woman presented with secondary amenorrhea of 14 months' duration following the rejection of her application for dental school. Physical examination revealed no abnormalities except for a small uterus. Height was 5 feet, 8 inches, and weight was 116 pounds (24 pounds underweight by Metropolitan Life tables). Weight had been stable for the past five years. Serum estradiol was low at 1.4 ng. per 100 ml. Basal serum FSH, LH, PRL, and T_4 were within normal limits (35 μg per 100 ml., 3.4 μg per 100 ml., 5.8 ng. per milliliter, and 4.6 μg per 100 ml., respectively.) However, mean LH levels during three hours of sampling every 20 minutes were very low (2.4 μg per 100 ml.). No value of LH during this observation period reached the mean normal LH levels for the follicular phase. Peak serum FSH and LH levels after the administration of 100 μg of LRF were attained at 60 and 45 minutes and were 110 and 35 μg per 100 ml., respectively. Administration of conjugated

*Ovral, Wyeth Labs., Div. American Home Products Corp., P. O. Box 8299, Philadelphia, Pennsylvania 19101.

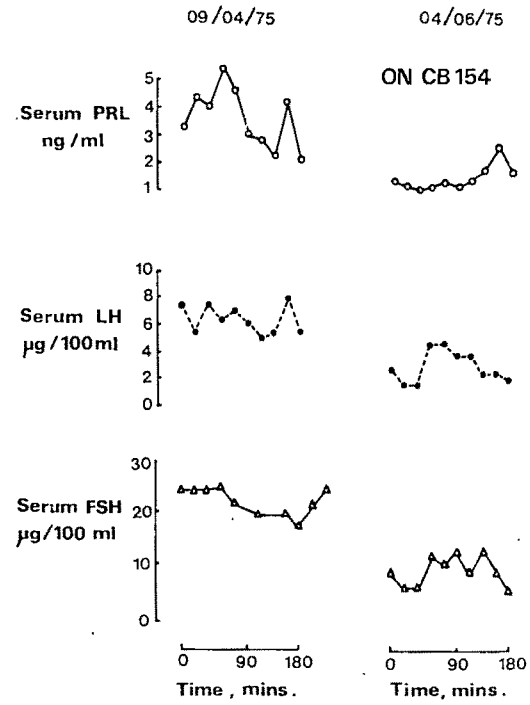


Fig. 1. Pulsatile pattern of serum concentrations of FSH, LH, and PRL before and during treatment with bromocryptine.

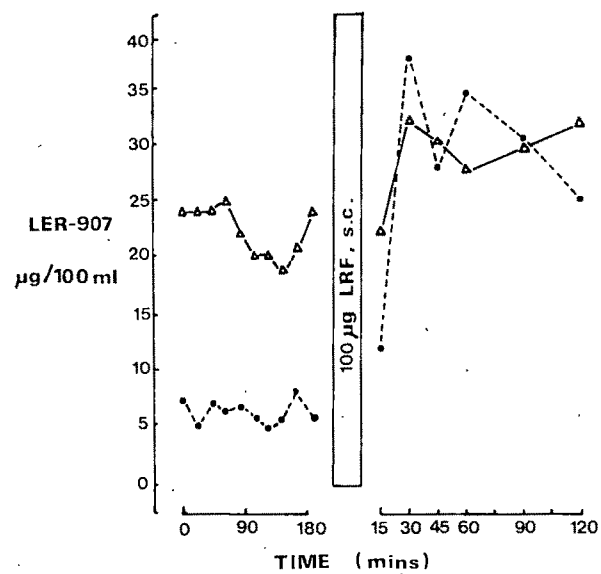


Fig. 2. Serum FSHΔ and LH (•) levels following the serum concentration administration of 100 μg of LRF.

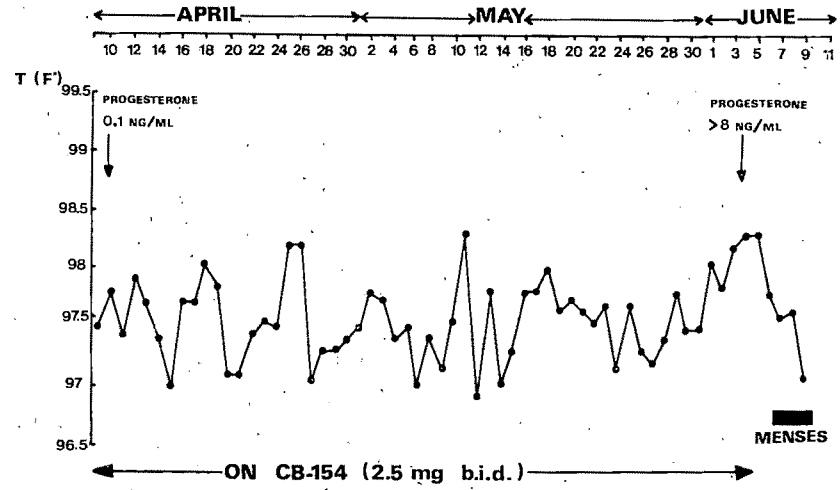


Fig. 3. Bromocryptine induction of ovulation in a patient with normoprolactinemic hypothalamic amenorrhea.

estrogens* and progesterone† in combination resulted in vaginal bleeding for three days. Clomiphene (200 mg. daily for seven days) was administered five days after bleeding and was followed by vaginal bleeding on Day 25. The BBT tracing remained monophasic, and progesterone levels, measured eight days prior to the day of vaginal bleeding, were in the follicular range (0.2 n. per milliliter). Eight weeks later, the BBT remained monophasic, and there had been no spontaneous vaginal bleeding. Bromocryptine was given in a dose of 2.5 mg. twice daily; 25 days later, vaginal bleeding occurred.

Comment

Hypothalamic or suprahypophyseal amenorrhea is characterized by: (1) basal serum gonadotropin levels which are normal or low, (2) adequate pituitary gonadotropin reserve, and (3) no evidence of pituitary tumor. The above three patients fulfil the criteria for that diagnosis. The presumed pathophysiology in these cases has been a fault in the release of endogenous LH/FSH–releasing factor. However, direct proof is lacking. The release of releasing factor(s) is most likely due to activation of peptidergic neurons by neurotransmitters, such as catecholamines.[6–8] Unavailability of catecholamines at the receptor site due to chemical competitors, i.e., phenothiazines, or false transmitters, i.e., alpha methyl-dopa, can lead to reversible amenorrhea of the suprahypophyseal type.[9] In addition to drugs, spontaneous hyperprolactinemia without associated demonstrable pituitary microadenoma is usually associated with amenorrhea.[10] Since such patients exhibit the above features, they are considered to have hypothalamic amenorrhea. In the group of hyperprolactinemic patients, the treatment of choice has utilized prolactin suppressants, i.e., levodopa and, more efficiently, bromocryptine. The mechansim of action of these drugs is not clear. It is possible that the excess prolactin turns off the endogenous secretion of gonadotropin-releasing factor since the removal of microadenoma is associated with a return of menstrual function in patients with microadenomas and excess prolactin secretion.[5] However, a direct central action of bromocryptine on the catecholamine receptors responsbile for peptidergic neuron activation has not been ruled out.[10, 11] The successful induction of menstruation and/or ovulation in the above euprolactinemic patients may illustrate such a possibility and open a new area in the treatment of hypothalamic amenorrhea syndromes.

*Premarin, Ayerst Labs.

†Provera, The Upjohn Co., 7171 Portage Rd., Kalamazoo, Michigan 49001.

REFERENCES

1. Yen, S. S. C., Rebar, R., Vanderberg, G., and Judd, H.: Hypothalamic amenorrhea and hypogonadotropinism. Responses to synthetic LRF, J. Clin. Endocrinol. Metab. **36:** 811, 1973.
2. Tolis, G., Cruess, S., Goldstein, M., and Friesen, H.G.: Survival and growth in a woman with untreated hypothalamic panhypopituitarism of 21 years duration, Can. Med. Assoc. J. **21:** 553, 1974.
3. Keller, P. J.: Treatment of anovulation with synthetic luteinizing hormone releasing hormone, Am. J. Obstet. Gynecol. **116:** 698, 1973.
4. Del Pozo, E., Varga, L., Wyss, H., Tolis, G., Friesen, H., Wenner, R., Vetter, L., and Uetwiller, A.: Clinical and

hormonal responses to Br-ergocryptine (SB-154) in the galactorrhea syndromes, J. Clin. Endocrinol. Metab. **39:** 18, 1974.
5. Friesen, H. G., and Tolis, G.: Canadian Cooperative Study: Effects of bromocryptine in 69 patients with galactorrhea-amenorrhea-hyperprolactinemia. Clin. Endrocrinol. In press.
6. Kalra, S. P., and McCann, S. M.: Effects of drugs modifying catecholamine synthesis on plasma LH and ovulation in the rat, Neuroendocrinology **15:** 79, 1974.
7. Sawyer, C. H., Hilliard, J., Kanematsu, S., Scaramuzzi, R., and Blake, C. A.: Effects of intraventricular infusions of norepinephrine and dopamine on LH release and ovulation in the rabbit, Neuroendocrinology **15:** 328, 1974.
8. Tima, L., and Flerko, B. L.: Ovulation induced by norepinephrine in rats made anovulatory by various experimental procedures, Neuroendocrinology **15:** 346, 1974.
9. Tolis, G., and Kolivakis, T.: On the mechanism of amenorrhea induced by neuroleptics and alphamethyldopa, Presented at the International Symposium on Hypothalamus and Endocrine Functions, Quebec City, 1975. New York, 1975, Plenum Press, Inc., pp. 32-33. (Abst. No. 38.)
10. Boyd, A. E., and Reichlin, S.: Galactorrhea amenorrhea bromergocryptine and the dopamine receptor, N. Engl. J. Med. **293:** 451, 1975.
11. Hokfelt, T., and Fuxe, K.: Effects of prolactin and ergot alkaloids on the tubero-infundibular dopamine neurons, Neuroendocrinology **9:** 100, 1972.

Plasma testosterone and dihydrotestosterone in ovulatory and anovulatory cycles

M. YUSOFF DAWOOD, M.D., CH.B., M.MED., M.R.C.O.G., F.A.C.O.G.
BRIJ B. SAXENA, PH.D.
New York, New York

Daily plasma testosterone (T) and dihydrotestosterone (DHT) as well as plasma luteinizing hormone, plasma estradiol (E_2) and plasma progestrone (P) were measured by radioimmunoassay in seven ovulatory cycles and in three anovulatory cycles. In ovulatory cycles, plasma T ranged from 110 to 637 pg. per milliliter, while plasma DHT ranged from 10 to 246 pg. per milliliter. There is an increase in the mean plasma T during the early follicular phase of the cycle with a fall on the day of ovulation. Plasma T levels rise again during the early luteal phase and drop during the late luteal phase of the cycle. Plasma E_2 rises during the follicular phase with a preovulatory surge followed by a drop after ovulation and a subsequent secondary rise. Plasma P was less than 1 ng. per milliliter during the follicular phase and increased to above 5 ng. per milliliter after ovulation, reaching levels of 20 to 25 ng. per milliliter during the luteal phase. In anovulatory cycles, there is random fluctuation with no well-defined patterns. Plasma P remained below 1 ng. per milliliter throughout the cycle. The finding of maximum T levels prior to midcycle may reflect increased T production by the ovaries in response to increasing levels of follicle-stimulating hormone. There is little fluctuation in the levels of T during the menstrual cycle. These findings obviate the need for multiple plasma T estimations in the assessment of women with hirsutism, polycystic ovarian disease, and the testicular feminization syndrome.

IT IS WELL ESTABLISHED that the ovary secretes androgens during the menstrual cycle,[1] and disruptions in the metabolism and/or production of androgens are associated with polycystic ovarian disease,[2,3] hirsutism,[3] and the testicular feminization syndrome.[4] In the human subject, estradiol (E_2) can be produced by aromatization of testosterone (T), but 5α-reduced androgens such as dihydrotestosterone (DHT) cannot be aromatized to estrogens. There is peripheral conversion of T to DHT. Investigations in rats have emphasized the control of luteinizing-hormone (LH) secretion at physiologic levels by androgens that are not aromatized to estrogens. DHT inhibits estradiol binding by engaging in low-affinity interactions which decreases the rate of formation of the estradiol-receptor complex.[5]

Recent investigations to establish the pattern of androgen fluctuation have focused attention mainly on T and/or androstenedione (A) and dehydroepiandrosterone (DHEA).[6-8] With the exception of the results of Auletta and associates,[6] T as measured in these studies usually included DHT as there was no attempt to separate these two androgens. In view of the relationship of T and DHT to estrogen levels and estrogen-receptor binding and the possible effect of feedback on gonadotropin release, measurements of T and DHT levels throughout the menstrual cycle in both ovulatory and anovulatory cycles would be important to permit more meaningful interpretation of plasma T and DHT levels. Androgen levels throughout anovulatory cycles have not been previously reported. This paper reports our study of circulating T and DHT during ovulatory and anovulatory cycles, in relation to other gonadal steroids and LH.

From the Department of Obstetrics and Gynecology, Cornell University Medical College.

Supported by National Institute of Health Grant No. HD 04173-10 and Ford Foundation Grant GT 670-0455.

Received for publication December 15, 1975.

Revised March 25, 1976.

Accepted April 9, 1976.

Reprint requests: Dr. M. Yusoff Dawood, Department of Obstetrics and Gynecology, 1300 York Ave., New York, New York 10021.

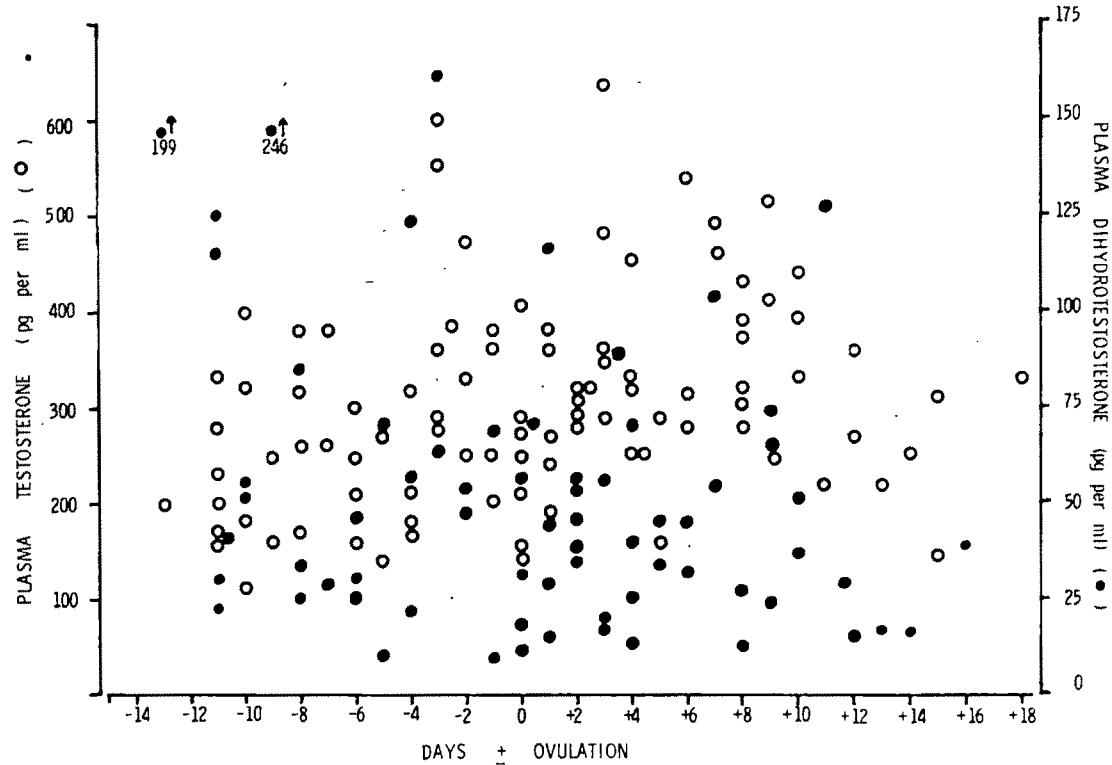


Fig. 1. Distribution of plasma T and DHT throughout seven ovulatory menstrual cycles dated against the day of ovulation (Day O).

Material and methods

Subjects. Ten cycles in seven healthy adult women, 20 to 40 years old, who were not using any form of hormonal contraception or receiving hormonal treatment were studied. All the subjects had normal working hours and regular menstrual cycles. Three of the cycles studied in two subjects lasted 35 to 38 days, while the other seven cycles had a duration between 22 and 28 days.

Daily basal body temperature was taken and recorded in each subject in each cycle studied. Blood was drawn daily around the midcycle or every other day when it was at the beginning or end of a cycle, at the same time each day, between 0900 and 1000 hours. The plasma was separated and stored at −20° C. until ready for hormonal assay. All the plasma samples from a subject were assayed for each hormone in a single run.

Hormonal assays. Plasma T and DHT were measured by radioimmunoassay as described by Auletta and associates.[6] Details of the modification as performed in our laboratory have been described previously.[9] The antibody used was raised in rabbits against T-17β hemisuccinate conjugated to bovine serum albumin. After 1 ml. of plasma was extracted with anhydrous ether, the extract was dried, and chromatography was performed on Sephadex LH-20 with the use of isooctane:benzene:methanol (95:5:5, v:v:v) as eluant to separate T and DHT. T and DHT were then measured by radioimmunoassay. All assays were carried out in duplicate, and procedural losses were monitored by addition of T 1,2-H^3(N).* All results were corrected for procedural losses. The intra-assay coefficient of variation was 9 per cent, and the interassay coefficient of variation was 13.8 per cent.

Plasma E_2 was measured by radioimmunoassay with the use of antiserum raised in sheep against estradiol-17β-6-(O-carboxymethyl) oxime coupled to bovine serum albumin. Details of the procedure as performed in our laboratory have been described before.[10] Procedural losses were monitored by addition of E_2-2, 4, 6, 7-H^3(N).† Recovery of E_2 was 79.4 ± 1.1 per cent.

Plasma P was measured by radioimmunoassay as previously described[11] with the use of antiserum raised in rabbits against P-11-oxime conjugated to bovine

*Specific activity, 44 Ci per millimole. New England Nuclear, 575 Albany St., Boston, Massachusetts 02118.

†Specific activity, 100 Ci per millimole. New England Nuclear.

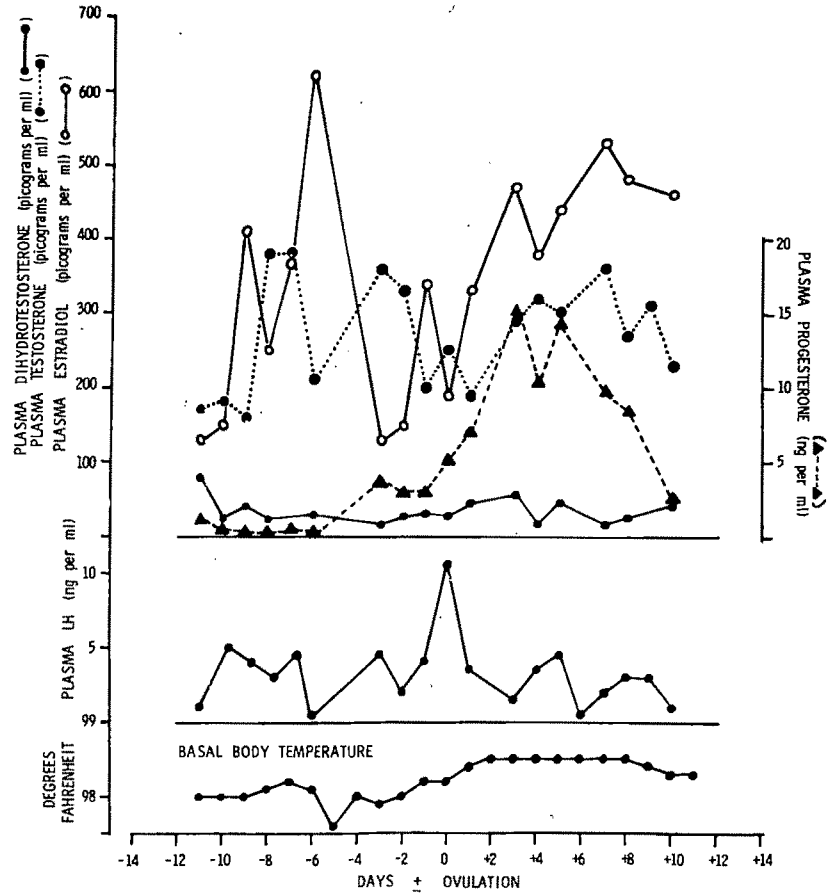


Fig. 2. Basal body temperature and plasma LH, E_2, P, T, and DHT throughout a normal menstrual cycle.

serum albumin. Procedural losses were monitored by the addition of P-1,2-H^3(N). All results were corrected for recovery. Intra-assay and interassay coefficients of variation were satisfactory.

Plasma LH was measured by radioimmunoassay as previously described.[12]

Results

Fig. 1 shows the distribution of plasma T and DHT throughout seven ovulatory cycles dated against the day of ovulation which was taken as the day of LH peak. The lowest concentration of plasma T was 110 pg. per milliliter, while the highest concentration was 637 pg. per milliliter. In contrast, DHT was present in much lower concentrations, ranging from 10 to 246 pg. per milliliter. With the exception of a few instances, most DHT levels were below 130 pg. per milliliter. There is a progressive rise in the mean concentration of T from the early follicular phase of the menstrual cycle to the late follicular phase followed by a drop on the day of ovulation (Table I). After ovulation, mean plasma T rose sharply and then decreased with the approach of menstruation. With DHT, there was again a drop in the concentration on the day of ovulation (Table I). However, the drop in T and DHT on the day of ovulation was not statistically significant.

When individual cycles were examined, in all seven cycles, there was a consistent drop in plasma T on the day of ovulation followed by a subsequent increase (Fig. 2). With DHT, such a consistent fall at the time of ovulation is not invariably noted. The pattern of plasma T, DHT, and E_2 levels in two patients with anovulatory cycles, as judged by (1) the absence of an LH peak, (2) a rise of progesterone, and (3) a monophasic basal body temperature pattern, is shown in Figs. 3 and 4. There was random but not marked variation in plasma T and DHT levels.

Plasma E_2 and P had similar values and patterns as previously reported by other investigators.[13] There was a rise in plasma E_2 during the follicular phase with a preovulatory peak followed by a sharp drop after ovulation and a secondary increase during the secretory phase. Plasma P was less than 1 ng. per milliliter during the follicular phase, increased to above 5 ng.

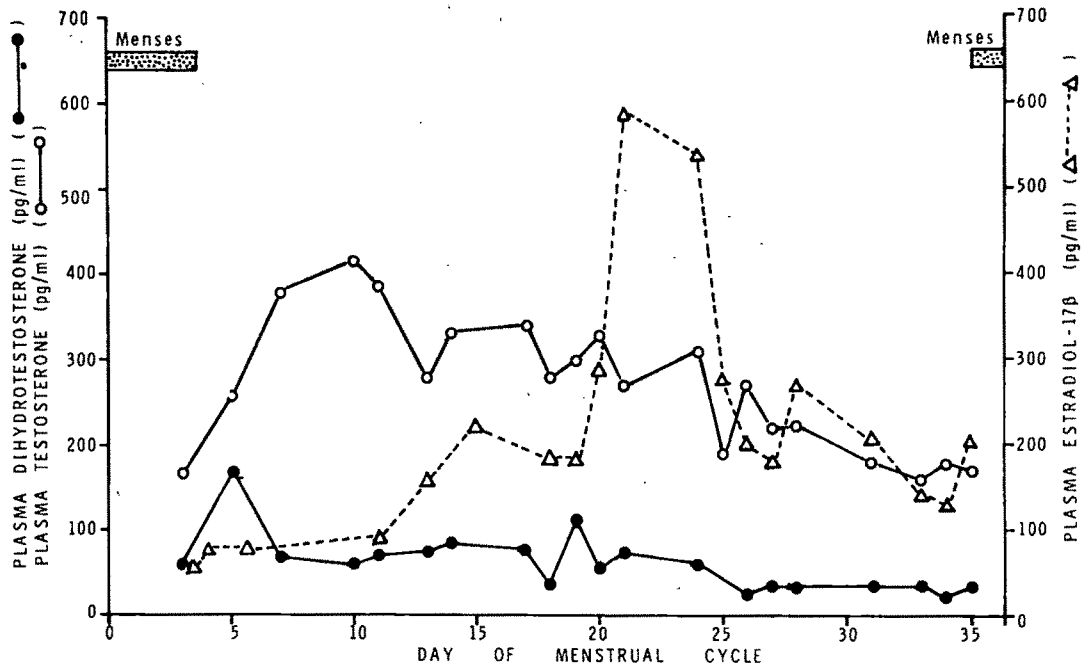


Fig. 3. Plasma T, DHT, and E_2 throughout a 35 day anovulatory cycle. This subject remained anovulatory for a year and reverted spontaneously to regular ovulatory cycles thereafter.

Table I. Plasma T and DHT concentrations grouped for different phases of ovulatory menstrual cycles

	Stage of menstrual cycle				
	*Early follicular phase**	*Late follicular phase*	*Day of ovulation (LH peak)*	*Early secretory phase†*	*Late secretory phase*
Plasma T (pg./ml.)					
Range	110-400	140-600	140-403	160-637	120-495
Mean ± S.E.	250.4 ± 19.7	297.1 ± 25.9	244.7 ± 34.1	326.6 ± 19.7	265.0 ± 20.1
Plasma DHT (pg./ml.)					
Range	14-246	10-90	11-71	13-117	13-129
Mean ± S.E.	70.6 ± 16.2	53.2 ± 10.8	38.4 ± 11.3	45.4 ± 5.1	48.6 ± 10.8

*Early and late follicular phase refers to the first and second halves of the follicular phase.
†Early and late secretory phase refers to the first and second halves of the secretory phase.

per milliliter after ovulation, and reached levels of 20 to 25 ng per milliliter during the secretory phase (Fig. 2). In anovulatory cycles, there is random fluctuation of plasma E_2 and plasma P remained below 1 ng. per milliliter.

Comment

The present study shows that plasma T ranged from 110 to 637 pg. per milliliter during normal ovulatory cycles. There was fluctuation in the circulating T levels at different phases of the menstrual cycle, but the difference in the means of circulating T levels at different phases of the menstrual cycle was not significant. The daily concentration of DHT during the menstrual cycle has not been reported before except for the mean levels during the follicular and secretory phases of the cycle.[6] In contrast to T levels, the concentration of DHT during the normal ovulatory cycle was much lower. Although there was a fall in the mean DHT level on the day of ovulation (Table I), the differences in the mean levels during the four quarters of the cycle and on the day of ovulation were not significant. When individual normal ovulatory cycles were examined, it was consistently observed that there was a fall in circulating T levels from the preovulatory levels on the day of ovulation. In individual cycles, there is much less fluctuation of DHT throughout the cycle.

Peripheral plasma A increased to a maximum of 2.3 ng. per milliliter on the seven days around mid-

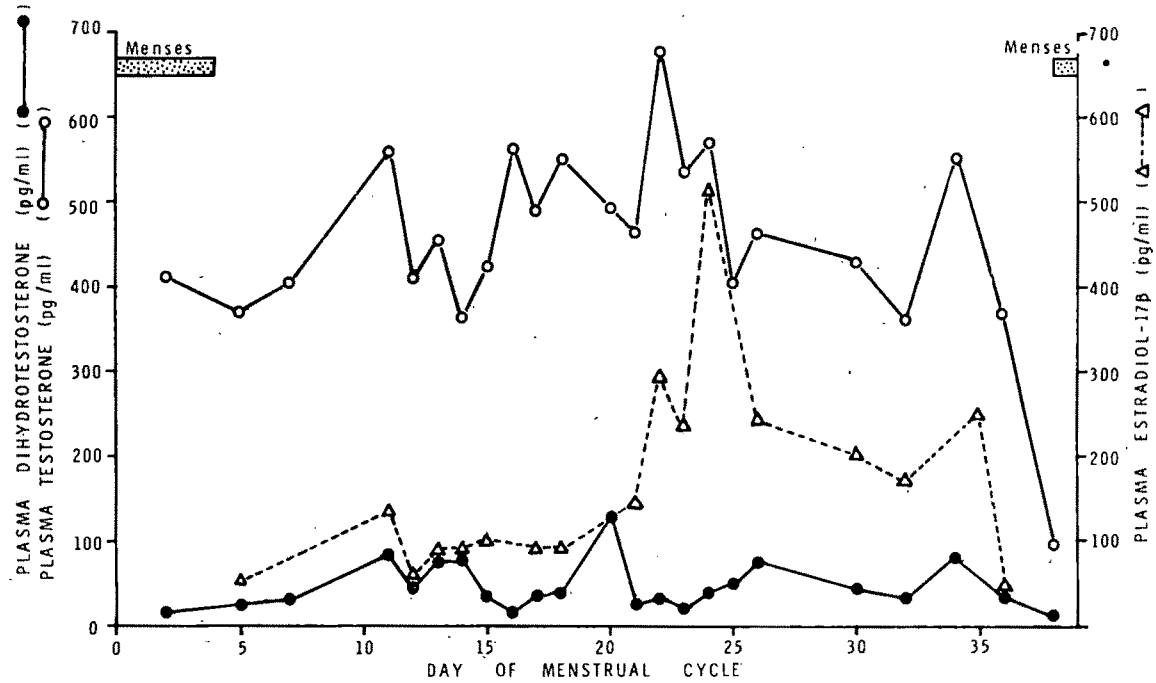


Fig. 4. Plasma T, DHT, and E_2 throughout a 38 day anovulatory menstrual cycle. This subject continued to have prolonged irregular anovulatory cycles for 18 months.

cycle[14] or at midcycle,[7] and 50 to 60 per cent of circulating T originates from peripheral conversion of A.[14] Our finding of an increase in peripheral plasma T to a peak level in the late follicular phase and a subsequent rise in T during the early luteal phase is consistent with these observations and with the findings of the highest T level around midcycle by Judd and Yen.[7] However, Coyotupa and colleagues[15] have found higher T levels in the luteal phase than during the follicular phase. Dupon and co-workers[16] found no such difference. The findings of peak levels of T prior to the midcycle may reflect increased production of T by the ovaries in response to increasing levels of follicle-stimulating hormone as well as extragonadal conversion of T to E_2. Increased testosterone levels have been noted in induction of ovulation with gonadotropins with evidence of mild hyperstimulation.[17]

Despite the above observations, the variability of circulating peripheral T levels during the normal menstrual cycle is well within a relatively narrow range to permit a reasonably valid evaluation of the plasma T level taken at any phase of the menstrual cycle in patients with hirsutism. However, other investigators[8] concluded otherwise because of the wide coefficient of variation. It may be relevant to point out that in idiopathic hirsutism, besides T levels, A levels and the androgen receptors (and thus androgen sensitivity) of the hair follicles are other important considerations.

Androgen levels throughout anovulatory cycles have not been reported before. Our findings showed essentially no consistent pattern in T and E_2 levels throughout anovulatory menstrual cycles, and DHT levels remained low with little fluctuation. Plasma P levels remained below 1 ng. per milliliter throughout anovulatory menstrual cycles. In ovulatory cycles, plasma P levels rose from 1 ng. per milliliter during the follicular phase to 5 to 25 ng. per milliliter during the secretory phase. Our findings on plasma E_2 and P were essentially similar to and confirm the findings obtained by other workers.[13]

REFERENCES

1. Gandy, H. M., and Peterson, R. E.: Measurement of testosterone and 17-ketosteroids in plasma by the double isotope dilution derivative technique, J. Clin. Endocrinol. Metab. **28:** 949, 1968.
2. Easterling, W. E., Talbert, L. M., and Potter, H. D.: Serum testosterone levels in the polycystic ovary syndrome, Am. J. Obstet. Gynecol. **120:** 385, 1974.
3. Bardin, C. W., and Lipsett, M. B.: Testosterone and androstenedione blood production rates in normal women and women with idiopathic hirsutism or polycystic ovaries, J. Clin. Invest. **46:** 891, 1967.

4. Judd, H. L., Hamilton, C. R., Barlow, J. J., Yen, S. S. C., and Kliman, B.: Androgen and gonadotropin dynamics in testicular feminization syndrome, J. Clin. Endocrinol. Metab. **34:** 229, 1972.
5. Mahesh, V. B., Muldoon, T. G., Eldridge, J. C., and Korach, K. S.: The role of steroid hormones in the regulation of gonadotropin secretion, J. Steroid Biochem. **6:** 1025, 1975.
6. Auletta, F. J., Caldwell, B. V., and Hamilton, G. L.: Androgens: Testosterone and dihydrotestosterone, *in* Jaffe, B. M., and Behrman, H. R., editors: Methods of hormone radioimmunassy, New York, 1974, Academic Press, Inc., pp. 359-370.
7. Judd, H. L., and Yen, S. S. C.: Serum androstenedione and testosterone levels during the menstrual cycle, J. Clin. Endocrinol. Metab. **36:** 475, 1973.
8. Goebelsmann, U., Arce, J. J., Thorneycroft, I. H., and Mishell, D. R.: Serum testosterone concentrations in women throughout the menstrual cycle and following HCG administration, Am. J. Obstet. Gynecol. **119:** 44, 1974.
9. Dawood, M. Y., and Saxena, B. B.: Serum testosterone and dihydrotestosterone in patients with trophoblastic disease, Obstet. Gynecol. **47:** 684, 1976.
10. Dawood, M. Y., and Ratnam, S. S.: Serum estradiol-17β in normal pregnancy measured by radioimmunoassay, Obstet. Gynecol. **44:** 194, 1974.
11. Morgan, C. A., and Cooke, I. D.: A comparison of the competitive protein binding assay and radioimmunoassay for plasma progesterone during the normal menstrual cycle, J. Endocrinol. **54:** 445, 1972.
12. Rommler, A., and Saxena, B. B.: Separation of antibody-bound and free human follicle-stimulating and luteinizing hormones by ethanol-ammonium acetate, Acta Endocrinol. **72:** 643, 1973.
13. Abraham, G. E., Odell, W. D., Swerdloff, R. S., and Hopper, K.: Simultaneous radioimmunoassay of plasma FSH, LH, progesterone, 17-hydroxyprogesterone and estradiol-17β during the menstrual cycle, J. Clin. Endocrinol. Metab. **34:** 312, 1972.
14. Baird, D. T., Burger, P. E., Heavon-Jones, G. D., and Scaramuzzi, R. J.: The site of secretion of androstenedione in non-pregnant women, J. Endocrinol. **63:** 201, 1974.
15. Coyotupa, J., Parlow, A. F., and Abraham, G. E.: Simultaneous radioimmunoassay of plasma testosterone and dihydrotestosterone, Anal. Let. **5:** 329, 1972.
16. Dupon, C., Rosenfield, R. L., and Cleary, R. E.: Sequential changes in total and free testosterone and androstenedione in plasma during spontaneous and clomid-induced ovulatory cycles, Am. J. Obstet. Gynecol. **115:** 478, 1973.
17. Schumert, Z., Spitz, I., Diamant, Y., Polishuk, W. Z., and Rabinowitz, D.: Elevation of serum testosterone in ovarian hyperstimulation syndrome, J. Clin. Endocrinol. Metab. **40:** 889, 1975.

Three-day therapy of vulvovaginal candidiasis with econazole: A multicentric study comprising 996 cases

J. A. BALMER, M.D.

Berne and Liestal, Switzerland

Within the scope of three open multicentric studies, effect and tolerability of 150 mg. econazole vaginal suppositories were tested in a total of 996 women, 13 to 74 years old (mean age, 29 years). Vaginal candidiasis had been mycologically demonstrated in every patient prior to therapy, and the total cure rate of 93.4 per cent in Studies I and II (880 patients) was also mycologically confirmed. The tolerability was tested by checking of 30 laboratory variables before and after the treatment of 116 patients (Study III); no therapy-related adverse changes were recorded. Connections between therapeutic results, age distribution, initial hormonal situation, and conception of the therapy are pointed out.*

MANY OF THE RECENTLY published papers discuss the problem of effective treatment of vulvovaginal candidiasis, which is on the increase.[3–5, 7, 12, 13, 18, 20] We do not always try to find reasons for the functional correlations between various personal concomitant factors (psychological, hormonal, pharmaceutical, and therapeutic in nature).[10, 12] It is the objective of this paper to present the results of a new three-day treatment with 150 mg. econazole vaginal suppositories.

Material and methods

The active substance econazole is a new antimycotic; its chemical name is 1-[2-(2,4-dichlorophenyl)-2-(4-chlorobenzyloxy)-ethyl]-imidazole nitrate (Fig. 1).[1] The following dosage forms of this antimycotic are already on the market: 1 per cent cream, 1 per cent spray solution, 1 per cent lotion, 1 per cent vaginal cream, and 50 mg. vaginal suppositories.

The range of action of the antimycotic econazole covers those of tolnaftate, nystatin, and benzylpenicillin sodium. Accordingly, it is effective against dermatophytes, yeasts (e.g., *Candida albicans*), dimorphous fungi, Actinomyces, and gram-positive bacteria.[17, 19] The effectiveness of econazole against candidiasis is superior to that of nystatin, and its effectiveness against dermatophytes is superior to that of tolnaftate.[19]

On the basis of available results of investigations into the ultrastructure of *Candida albicans* in vitro with econazole, and according to the biochemical findings on the treatment of yeast cells with the same fungicide or with substances of a similar chemical structure, the pathologic process can be assumed to take the following course: The primary effect of the fungicidal substance is based on changed permeability of the cell wall which is electron optically not perceptible.[16, 21] The fungicide penetrating into the cell inhibits the ribonucleid acid and protein syntheses. This process manifests itself in the formation of lytic areas in the cytoplasm. In the further course of the pathogenic process, the lipid metabolism is inhibited; finally, this reaction induces decomposition of the intracytoplasmic membrane systems and deposition of lipid-containing metabolic end products in the mitochondria. Thirty hours following the addition of 10 μg per milliliter of econazole (2.2×10^{-5}M), no more reproductive cells can be demonstrated. All components of the protoplast have lysed to a more or less advanced degree.[15, 16]

The clinical studies were performed within the scope of three trials which were independent of each other; they involved a total of 996 patients.

From the Gynecological Hospital of the University, Berne, and the Department of Obstetrics and Gynecology, Cantonal Hospital, Liestal.

Received for publication March 15, 1976.

Revised July 20, 1976.

Accepted July 27, 1976.

Reprint requests: Dr. J. A. Balmer, Department of Obstetrics and Gynecology, Cantonal Hospital, CH-4410 Liestal, Switzerland.

**Trademark in Switzerland: Gyno-Pevaryl 150 Combipack, Cilag-Chemie Ltd., Schaffhausen, Switzerland.*

Study I: 458 patients; two courses of treatment; follow-up examination at one week after termination of the therapy.

Study II: 422 patients; two courses of treatment; follow-up examinations at one and four weeks after termination of the therapy.

Study III: 116 patients; one course of treatment; follow-up examination at one week after termination of the therapy (safety evaluation).

Study I (458 patients) plus Study II (422 patients); total = 880 patients. Within the scope of clinical gynecologic examinations, samples of vaginal native preparations were taken from the patients regardless of whether or not they possibly complained of colpitis (patients with trichomoniasis were thus eliminated). Subjective symptoms such as vaginal burning, pruritus, and/or discharge and the identification of Candida in the vaginal native preparation in Nickerson's medium before initiation of treatment established the diagnosis of *Candida albicans* infection. Mycologic fungus demonstration prior to therapy was positive in a total of 996 patients (Studies I to III).

Except for hormonal contraceptives, no drugs were used, either topically or systemically, during or after the therapy with econazole. Cohabitation during or immediately before the treatment was not prohibited. The patients were treated with one 150 mg. econazole vaginal suppository once a day for a period of three consecutive days. In a few instances, the partners were treated with 1 per cent econazole cream.

To prevent residues of the drug from interfering with the cultures of fungi, an interval was allowed between the termination of the therapy and the check-up with Nickerson's medium. Thus, the mycologic test for evaluation of the therapeutic result was not repeated earlier than eight to 10 days after the last application of the drug.

The clinical results were based on mycologic identification of the fungi and on the effect of the substance on the following symptoms, which were: vaginal burning, vaginal pruritus, and vaginal discharge.

A second three-day course of treatment followed the first course for those patients who after the first three-day course of therapy had positive clinical findings and positive mycologic fungus identification. After another interval of at least one week, these patients underwent repeat clinical examination with mycologic fungus identification.

Since the initial hormonal situation has, according to the literature,[12] some influence on the therapeutic result, breakdown of the 882 (93.4 per cent) cured patients was made according to the following criteria:

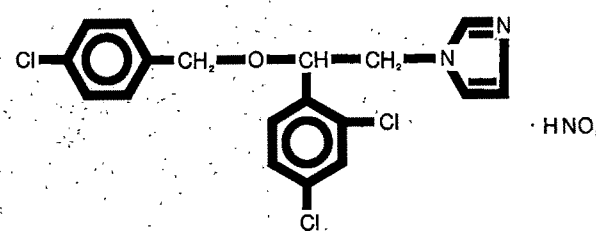


Fig. 1. Structural formula: Econazole nitrate.

pregnancy, hormonal contraception, or hormonal balance (neither pregnancy nor contraception); the significance of the percentages was then calculated.

Study II (422 patients). In this study comprising 422 patients, the rate of reinfection or relapse, respectively, was determined in addition. Aside from the usual mycologic fungus demonstration in Nickerson's medium at eight to 10 days after termination of the first or second course, respectively, of treatment with 150 mg. econazole vaginal suppositories, a further culture in Nickerson's medium was started at four weeks after the first or second course, respectively, of treatment.

Study III (116 patients). Within the scope of safety evaluation, the tolerability of 150 mg. econazole vaginal suppositories was tested in 116 of the total of 996 women with mycologically demonstrated candidiasis. Among others, 30 various laboratory variables (hemogram, chemogram, and leukocyte differential) were measured before and after the treatment and, eventually, statistically evaluated.

The significance was calculated with the chi-square test.

Results

Studies I to III. The age distribution of the 996 patients involved in Studies I to III is illustrated in Fig. 2. This diagram shows that the ages of the test population involved in these studies were comparable; the group 20 to 34 years old (66 per cent) predominated. The patients' ages ranged from 13 to 74 years (mean age, 29 years).

Within the scope of these three studies, 112 pregnant women were treated with 150 mg. econzaole vaginal suppositories. Study I included 48 patients; Study II, 60 patients; and Study III, four patients. On the basis of retrospective investigations, more detailed data during the course of 111 pregnancies were gathered. No report on the remaining case is available. Of the 111 pregnancies, three ended with abortions and three patients had elective interruptions, while six patients failed to reappear for examination. The other pregnant women gave birth to 99 healthy

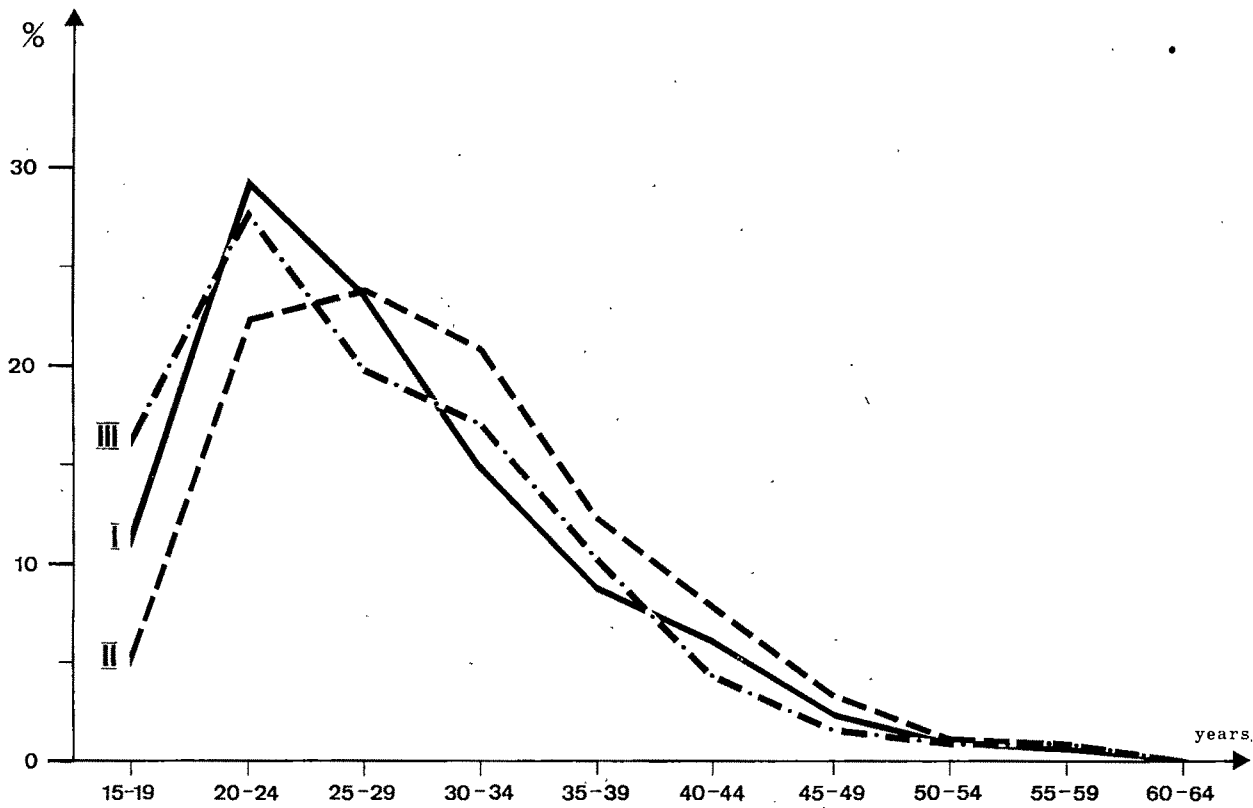


Fig. 2. Age distribution in Studies I to III. Study I, ——; Study II, -------; Study III, - - - - - - -.

Table I. Mycologic demonstration of the effectiveness of 150 mg. econazole vaginal suppositories: Summary of Studies I and II

Study	Patients (No.)	Cured				Not cured	
		First course (No.)	Second course (No.)	Total			
				No.	%	No.	%
I	458	392	28	420	91.7	15 + 23*	8.3
II	422	349	53	402	95.3	20	4.7
Total	880	741	81	822	93.4	35 + 23*	6.6

*Data not available.

Table II. Frequency of vaginal concomitant symptoms and therapeutic results

Symptom	Frequency of symptoms (%)	No. of patients	% of patients	Symptoms eliminated	
				No.	%
Vaginal burning	75.5	664	100	562	84.6
Vaginal pruritus	89.7	789	100	659	83.5
Vaginal discharge	96.9	853	100	402	47.1

babies. No malformations were observed. Body weights and heights were within the normal range. Of the newborn infants, 55 were boys and 44 girls. One baby developed postnatal oral candidiasis.

No subjective intolerance or adverse reactions were observed in the 996 patients; neither were there objective changes in clinical laboratory values or blood chemistry indicative of side effects.

Studies I and II. A summary of the results, obtained in a population of 880 women (Studies I and II) with positive mycologic fungus identification in Nickerson's medium prior to treatment, is shown in Table I. In order to establish the total cure rate of 93.4 per cent, the cures in Groups I and II were added, and the 23 patients who failed to return for their second course of treatment as well as the uncured cases were evaluated. The differentiated breakdown of the results, separately for Study I and Study II, is also given in Table I.

The frequency of concomitant vaginal symptoms (burning, pruritus, and discharge) is illustrated in Table II; it appears that almost all of these 880 patients, that is, 96.6 per cent, suffered from dis-

Table III. Influence of the initial hormonal situation on the effectiveness of the treatment

Studies I and II	Patients (No.)	Cured				Not cured	
		First course (No.)	Second course (No.)	Total			
				No.	%	No.	%
Pregnancy	108	79	17	96	88.9	6 + 6*	11.1
Hormonal contraception	345	304	26	330	95.7	11 + 4*	4.3
Hormonal balance	427	358	38	396	92.7	18 + 13*	7.3
Total	880	741	81	822	93.4	35 + 23*	6.6

*Data not available.

charge. The frequency of the other two symptoms was lower.

The concomitant vaginal symptoms, burning and pruritus, were cured with 150 mg. econazole vaginal suppositories in about 84 per cent of the cases. Unlike these two symptoms, discharge responded to the treatment in no more than 47 per cent of the cases because, as is generally known, this symptom can also be caused by other diseases which cannot be cured by an antimycotic (Table II).

Differentiation of the cure rates for all 880 patients according to the initial hormonal situation failed to reveal significantly different values in the chi-square test (Table III).

The highest failure rate of 11.1 per cent was found in the group of pregnant patients. On the other hand, the lowest percentage (4.3 per cent) of uncured cases was found in the group of patients using hormonal contraceptives. These two failure rates are significantly different ($p < 0.01$). The third group, on which neither exogenic nor endogenic influences were exerted (hormonal balance), was—with 7.3 per cent of refractory cases—roughly between the two extreme values (Table III).

Study II. Three hundred and forty-nine patients were cured after the first course of treatment, and 53 were cured after the second course of treatment. Thus, the cure rate for 422 patients was 95.3 per cent. Relapse or reinfections, respectively, were demonstrated by means of the Nickerson's medium test in 46 patients at four weeks after termination of the therapy (Table IV).

Study III. The parameters checked in 116 cases failed to reveal statistically significant changes in 26 of the 30 tested laboratory variables. Significant mean changes were observed, with an error probability of less than 5 per cent, for only four laboratory values (erythrocytes, hemoglobin, calcium, and monocytes); the mean values for these four variables were within the normal range. However, erythrocytes, hemoglobin, and calcium failed to show significant changes in the McNemar test. A significant increase revealed by the McNemar test, with an error probability of 5 per cent, was obtained only for monocytes.

Table IV. Rate of reinfections or relapse for 422 patients

	First course of treatment		Second course of treatment		First and second course of treatment	
	No.	%	No.	%	No.	%
Patients	422	100	73	17.3		
Cured cases at first checkup at one week after termination of therapy	349	82.7	53	12.6	402	95.3
Cured cases at second checkup at four weeks after termination of therapy	308	73.0	48	11.4	356	84.4
Reinfection or relapse	41	9.7	5	1.2	46	10.9

Comment

The results obtained demonstrate that the variety of drugs available for the treatment of vulvovaginal mycoses has now been enriched by another effective preparation.[1, 8, 14] As compared with cure rates of 60 to 85 per cent obtained with conventional drugs,[2, 5, 9, 11] mycologically confirmed cure rates of 93.4 per cent were obtained with 150 mg. econazole vaginal suppositories. The cures were not judged by the absence of complaints or the negative native preparation but by the negative result of the specific Candida cultures.

It is generally known that vaginal burning, pruritus, and discharge are not as well controlled by antimycotic treatment as is candidiasis. This can be explained by the fact that, according to experience, these symptoms are not triggered by Candida infection alone but can

also be caused by other factors (local factors, systemic factors, diabetes mellitus, pregnancy, an exogenous gestagen supply such as from hormonal contraceptives, etc.); however, these factors can not be causally influenced by a specific and exclusively antimycotic treatment.

The respective interaction between pathophysiology and the mechanism of action of vulvovaginal infections has been dealt with sufficiently in the medical literature. In particular, the correlations between the given hormonal situation and the frequency of candidiasis have been established.[3, 4]

The same pathophysiologic mechanisms which induce higher infection rates (alcalization of the pH, indirect inhibition of the glycogen catabolism by progesterone, etc.) offer possibilities of improving the effectiveness of treatment, provided these mechanisms are eliminated. At the moment, however, it cannot be stated how an applied hormone combination would influence the therapeutic result by its estrogenic or gestagenic, respectively, character. With consideration of the current preferred tendency toward a decrease in the progestogen component of commercial hormonal contraceptives, it is possible that an improvement in the environment has already been obtained. The cure rate for pregnant patients (gestagenic hormonal situation) is about 10 per cent lower after one course of treatment and about 7 per cent lower after two courses than for patients using hormonal contraceptives. A global evaluation of the results, with consideration of the population uninfluenced by hormones, is not possible at present because the initial hormonal situation of this third group and its influence on the vaginal environment cannot be judged.

As to morbidity, an apparent concentration at the age of 20 to 34 years (66 per cent of the patients) can be proved. However, the majority of patients receiving hormonal contraceptives and pregnant women belong to this age group. These facts, too, indicate pathogenetic correlations between hormonal balance and vulvovaginal infections.

The significant increase in the mean percentage of monocytes, observed in Study III (116 patients), is interpreted as a phase of "monocytic defense or overcoming" of the mycotic infection. According to Schilling's typical biological leukocyte curve, the monocytes increase in cases of acute infection or mycoses, respectively, from about Day 5 to Day 7.[6] The therapy requiring only three days offers decisive advantages primarily for self-willed patients who often tend to discontinue the therapy prematurely, contrary to different instructions, especially when the subjective symptoms subside. According to experience, patients see their doctors because of the subjective symptoms of candidiasis such as burning, pruritus, and discharge: however, if these symptoms are absent, candidiasis is not diagnosed in some patients until the occasion of an annual routine examination. In particular, those symptoms which are not believed to be disturbing, subside during treatment, or are even completely absent lead to the following three principles:

1. The very possibility of prescribing various dosage forms of a given drug can have considerable influence on the completion of the treatment, as a therapeutic method can be chosen which is adequate to the individual patient's mentality.[1, 9, 12]

2. Optimum therapeutic results mainly depend on how categorically and consistently the physician points out to the patient that the prescribed therapy must be carried out strictly and completely.

3. Regular and correct completion of the therapy by the patient herself decisively depends upon the required duration of treatment with the chosen drug.[1, 12]

Necessary concomitant treatment of all possible sources of reinfection, e.g., vulva, anal region, perineum, and, if necessary, the partner, is made easier by simultaneous use of 1 per cent econazole cream.

Multicentric studies with 150 mg. econazole vaginal suppositories showed that despite the minimum duration of the treatment (only three days) this drug was highly efficient. Because of the extremely short duration of the therapy, the patient is considerably less stressed than when conventional long-term methods are employed. With the use of this extremely short therapy, the coincidence of subjective or objective adverse circumstances (menstruation, traveling, holidays on the beach, etc.) can be avoided in the simplest possible way.

We wish to thank the colleagues who carried out the studies for permission to publish their results.

REFERENCES

1. Balmer, J. A.: ARS Med. **5:** 195, 1976.
2. Clow, L. R.: Can. Med. Assoc. J. **86:** 449, 1962.
3. Eimer, H.: Geburtshilfe Frauenheilkd. **32:** 221, 1972.
4. Eimer, H.: Geburtshilfe Frauenheilkd. **33:** 790, 1973.
5. Girotti, M., and Hauser, G. A.: Ther. Umsch. **25:** 308, 1968.
6. Gross, R.: Klin. Gegenwart **10:** 572, 1975.

7. Itani, Z. S.: Z. Haut. Geschlechtskr. **49:** 16, 683, 1974.
8. Keller, K.: Schweiz. Rundsch. Med. **63:** 722, 1974.
9. Martins, A. D.: An. Acad. Bras. Ginecol. **63:** 209, 1967.
10. Masterton, G., et al.: Br. Med. J. **1:** 712, 1976.
11. Nathanson, E. A.: Obstet. Gynecol. **16:** 601, 1960.
12. Obolensky, W., et al.: Dtsch. Med. Wochenschr. 35, 1730, 1975.
13. Peeters, F., Snauwaert R., Segers, J., van Cutsem, J., and Amery, W.: Am. J. Obstet. Gynecol. **112:** 80, 1972.
14. Peios, E.: Schweiz. Rundsch. Med. **64:** 1261, 1975.
15. Preusser, H.-J.: Mykosen **18:** 453, 1975.
16. Preusser, H.-J.: Mykosen, August/September, 1976. In press.
17. Schaer, G., et al.: Chemotherapie **22:** 211, 1976.
18. Schoyerer, W., and Thieme, R.: Aerztl. Prax. **23:** 2774, 1971.
19. Thienpont, D., et al.: Arzneim. Forsch. **25:** 224, 1975.
20. Wenzel, K.: Schweiz. Rundsch. Med. **65:** 287, 1976.
21. Zimmermann, F. K.: Presented at the VIth Congress of the International Society for Human and Animal Mycology, Tokyo, June 29–July 4, 1975.

Familial allergic seminal vulvovaginitis

TE-WEN CHANG, M.D.

Boston, Massachusetts

Vulvovaginal reactions to seminal fluid occurred in all four women in a family. The reactions consisted of stinging, burning, and pain in the vagina, starting during coitus or immediately after ejaculation, and persisting for 2 to 72 hours. The vagina and vulva were red and swollen, with urticaria on the labia. Although skin tests showed a positive reaction in two of three women tested, no sperm agglutination antibody was detected. Benadryl was effective in preventing the development of vulvovaginal reactions completely in one woman and partially in two others.

SEVERE FORMS of allergic reactions to semen have been reported on only two occasions. Generalized urticaria involving the skin, tongue, pharynx, and eyelids, together with asthmatic attack, occurred in a 29-year-old woman immediately following her first intercourse. The vaginal mucosa was congested. Pelvic pain was noted and uterine contractions were experienced. These reactions reached the peak within 15 to 30 minutes following ejaculation and persisted for about 24 hours.[1] A less severe form of allergy to semen was described in another woman who developed perivaginal and periorbital edema and a choking sensation in the throat several hours following coitus. These symptoms lasted for several days.[2] The present communication describes a still milder form of allergy to semen, occurring in all women in a family. Since these reactions are limited primarily to the perineal area, the term "familial allergic seminal vulvovaginitis" is proposed. Preventive measures are also described.

Methods

Preparation of skin test antigen. Fresh semen was collected by masturbation into a sterile container. The specimen was placed at room temperature for 30 minutes, allowing liquefaction of the seminal fluid to take place. The sperm was removed by centrifugation at 25,000 r.p.m. in a refrigerated centrifuge. Decimal dilutions of the seminal plasma were made in saline. Merthiolate 1:10,000 was added as preservative.

From the Tufts-New England Medical Center.

Received for publication March 15, 1976.

Accepted April 9, 1976.

Reprint requests: Te-Wen Chang, M.D., New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111.

Skin test. Both scratch and prick tests were performed with 10-fold dilutions of seminal plasma. Saline was used as control. Positive reaction consisted of wheal-and-flare on an erythematous base, which appeared within 3 minutes of application. Six young women were tested. All gave a negative response.

Serological tests. Mixtures of patient's serum dilutions and fresh sperm suspension were observed microscopically for motility and clumping following incubation at 37° C. for 5, 10, 20, 30, 60, 90, and 120 minutes. The serums were diluted twofold serially prior to use.

Clinical features

There were four women in the family. All had experienced discomfort from contact with seminal fluid, beginning from their first sexual intercourse. The mother, who had not been sexually active for the past several years, recalled that she could not tolerate coitus more frequently than once every third day because of local reactions following each ejaculation. She had three daughters. The oldest was married and had two children. All had a history of other allergies (hay fever, food allergies, etc.).

The first patient (age 24) was referred to the Clinics of the New England Medical Center Hospital because of recurrent genital herpes. She also gave a history of stinging, burning, and pain in the vagina during and following each coitus. The vagina and vulva were red and swollen, with urticarial lesions on the vulva. On several occasions, she noted that urticarial lesions developed on the chest or other parts of her skin when in direct contact with the semen. Immediately following ejaculation, she had to rush to the shower to wash off the ejaculate. Invariably, she noted a thin discharge from the vagina the next morning. During a period of

several months, when a condom was used, she was free from any reactions from coitus. Skin testing with seminal plasma was positive at a concentration of 10^{-3}. Her serum neither immobilized nor caused agglutination of fresh human sperm. Benadryl, 25 mg. orally, 30 minutes prior to coitus, was effective in preventing the development of these reactions. Local application of hydrocortisone reduced the severity of local reactions, but added discomfort by creating dryness of the vaginal mucosa. She had been on Benadryl prophylaxis for a period of 3 months during which she was free of discomfort following coitus except on occasions when the drug was not available. Following this, however, she stopped Benadryl entirely. To her surprise, vulvovaginal reactions to semen did not return.

The second patient (age 26) was requested to visit the New England Medical Center Hospital because of discomfort after each coitus. Stinging, burning, and pain were experienced immediately after ejaculation. She noted that her vagina and vulva were red and swollen, with urticaria on the labia. On one occasion, she suddenly felt "helpless with her body and lower extremities" during coitus, which was interupted immediately. She lay motionless for about half an hour and had to be carried to bed by others. She felt dizzy, but never lost consciousness. Skin testing showed a positive reaction to a 10^{-3} dilution of the seminal plasma. Serological tests were negative for sperm immobilization and agglutination. Benadryl and Chlor-Trimeton prophylaxis was partially effective in relieving vulvovaginal reactions. Local application of hydrocortisone also gave some relief, but its application created additional discomfort from lack of vaginal secretion during intercourse.

Patients 3 and 4 were not seen because both lived in other states. A list of questions was sent to each individual. Table I summarizes all pertinent information. A skin test kit was sent to John Kent, M.D., of Buffalo, New York, for Patient 4 (age 68).

Patients 1 and 2 had been taking birth-control pills since the beginning of their sexual activity.

Table I. Symptoms and signs of allergic seminal vulvovaginitis

	Age (yr.)			
	24	*26*	*33*	*68*
Onset of symptoms				
During intercourse	+*		+	
Immediately after ejaculation		+		+
Pain in vagina	+	+	−	−
Burning and stinging in vagina	+	+	+	+
Pelvic pain	+	−	−	−
Red and swollen vagina and vulva	+	+	+	+
Urticaria on vulva	+	+	−	−
Immediate shower	+	−	+	−
Discharge in the next morning	+	−	+	−
Duration of discomfort	24°	24°	Until shower	72°
Skin test	+	+	ND	−
Sperm agglutination antibody	−*	−	ND	ND
Prevention by antihistamine	+	±*	±	ND
Prevention by condom	+	ND*	ND	ND
Other allergies	+	+	+	+

*+, Yes or positive; −, no or negative; ±, partial; and ND, not done.

Comment

Allergy to human semen is a rare condition. Only two cases have been recorded in the literature.[1, 2] However, the actual incidence is not known because most physicians and the public are not aware of its existence. Patient 1 (age 24) had repeatedly told her gynecologist in a university hospital about her symptoms which were recorded in the medical record as "deep dyspareunia," but no further investigation was attempted. Her mother had experienced difficulties related to coitus all through her life, but considered it "a normal phenomenon."

The onset of stinging, burning, or pain may begin during coitus or immediately after ejaculation. It has been found that the prostatic or seminal vesicular fluids are as potent as regular seminal fluid in elicitating skin reactivity, suggesting that the prostatic or seminal fluid is responsible for the allergic reactions.[2] When the symptoms began during coitus, their partners were often told to hurry up because of the discomfort. Immediately after ejaculation, they rushed to the shower to wash off the seminal deposits.

The duration of vulvovaginal reactions to seminal fluid varied from 2 to 72 hours. Within these periods, coitus was not without pain from the beginning of penile penetration. Besides local symptoms, one patient (age 26) experienced a severe systemic reaction during coitus. Unfortunately, it was not possible to determine the type of reaction. It is of interest that the same man had had repeated coitus with her before and after the episode. The only reactions noted were those limited to the genital tract.

Skin testing with seminal plasma was positive at a concentration of 10^{-3}, which is weaker than those with systemic manifestations.[1, 2] The skin test was negative in the oldest patient, who had not had coitus for several years due to her husband's illness. It is possible that the

negative reaction could be related to the prolonged abstinence.

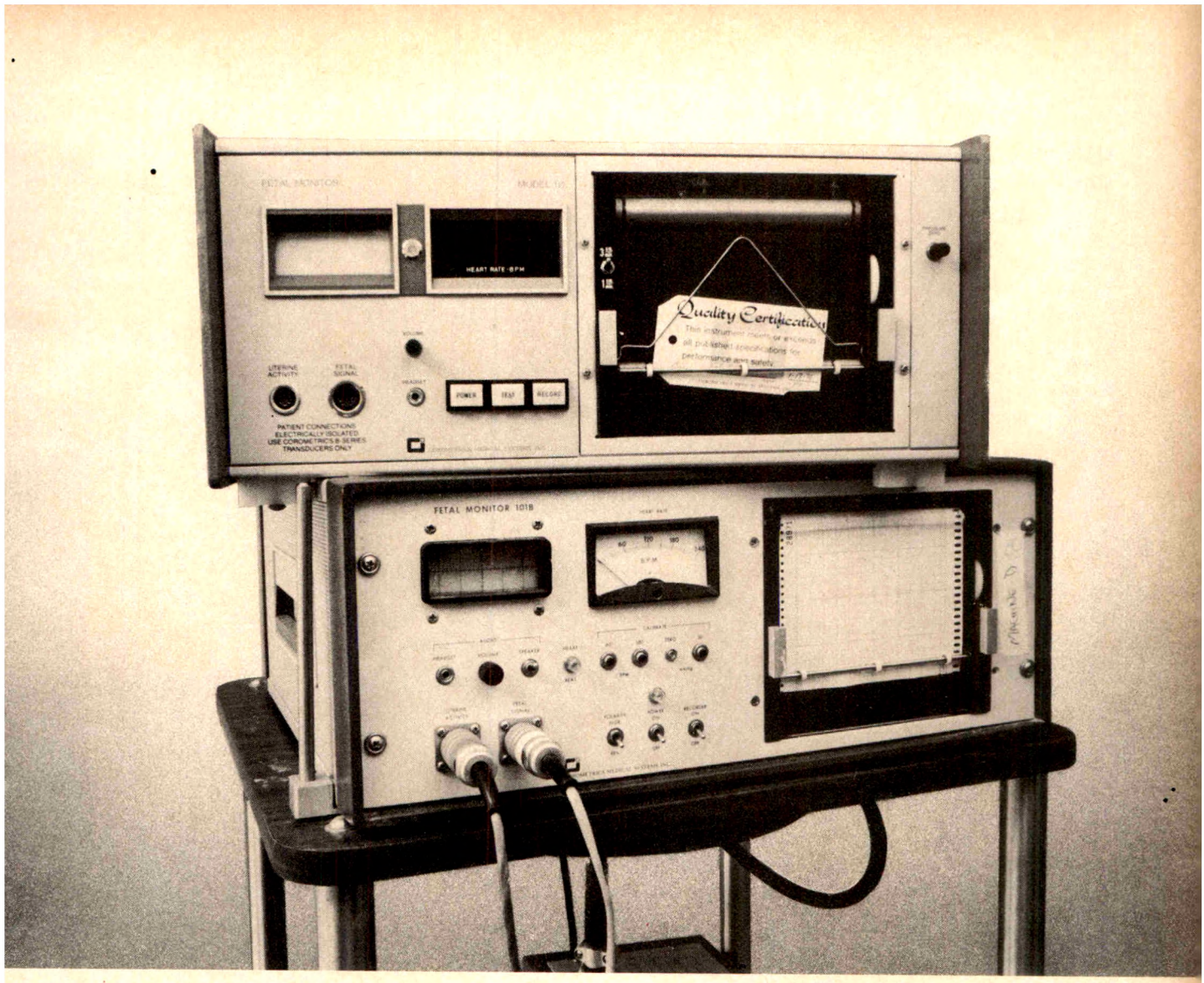
No sperm agglutination antibody was detected. These patients have no problems in fertility. Other reports also indicated the same.[2]

Response to antihistamine prophylaxis is a gratifying experience. Benadryl, 25 mg. given 30 minutes prior to coitus, was effective to prevent all the discomfort associated with seminal deposition in one woman. It was partially effective in others. The one who gave the best response stopped the drug entirely after 3 months' trial. Vulvovaginal reactions to semen did not reappear. Whether it represents a desensitization phenomenon is unclear. Desensitization was not successful in the reported cases.[1, 2]

REFERENCES

1. Halpern, B. M., Ky, T., and Robert, R.: Clinical and immunological study of an exceptional case of reaginic type sensitization to human seminal fluid, Immunology **12:** 247, 1967.

2. Levine, B. B., Sriaganian, R. P., and Schenkein, I.: Allergy to human seminal plasma, N. Engl J. Med. **288:** 894, 1973.



NUMBER ONE IS STILL HARD AT WORK.

Corometrics® 101 Fetal Monitor (serial number 101118001) has undergone some changes since its 1969 installation in New York Metropolitan Hospital. And it isn't tired yet.

In 1971, it was modified to 101A monitor specifications, providing more flexibility. Then, in 1973, the front panel and other internal changes made it a 101B, capable of both direct and indirect monitoring.

That same quality, integrity and reliability that went into the 101 Fetal Monitor seven years ago are found in the 111 Fetal Monitor today. Our Service Department can update your instrument to provide you with the latest state-of-the-art modifications. Our national network of Sales Consultants and Service Engineers are available to help you with your individual requirements. For expansion of present equipment, our Systems Department can provide you with many options engineered to individual specifications. And for education in the practical applications of monitoring, Corometrics RN Perinatal Specialists periodically conduct community workshops throughout the year.

It's all part of our Total Product Support. Our customers are Number One. And we're working hard to keep it this way.

COROMETRICS MEDICAL SYSTEMS, INC.
Barnes Industrial Park
Wallingford, Connecticut U.S.A. 06492
Telephone: [203]265-5631 Telex: 940 403

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY

TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.

A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

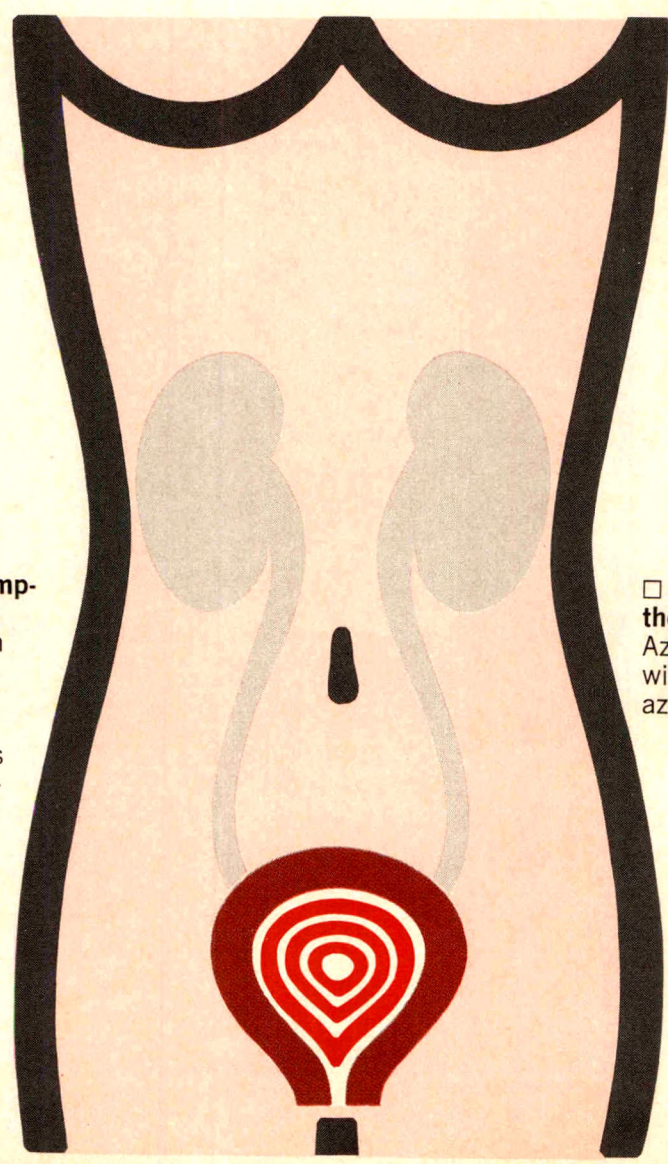
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

When pain complicates acute cystitis*

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain for the pathogens



☐ **Early relief of painful symptoms** such as burning and discomfort associated with urgency and frequency.

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

☐ **Appropriate antibacterial therapy:** up to three days with Azo Gantanol, then 11 days with Gantanol® (sulfamethoxazole).

*nonobstructed; due to susceptible organisms

ROCHE

WHAT'S GOOD FOR THE DIFFICULT-TO-TREAT PATIENT...

IS ALSO GOOD FOR THE ROUTINE VAGINAL CANDIDIASIS PATIENT

© OPC 19

After a single course of treatment (once daily, h.s., for 14 days)

Patients	Symptomatic relief	Cure rate
Pregnant women†	89% (159 of 179 patients)	84% (151 of 179 patients)
Non-pregnant women	85% (203 of 239 patients)	80% (192 of 239 patients)
Women on antibiotic therapy	81% (17 of 21 patients)	81% (17 of 21 patients)
Women previously treated one or more times with other antifungal agents	83% (148 of 179 patients)	77% (137 of 179 patients)
Totals	87% (362 of 418 patients)	82% (343 of 418 patients)

The criteria for "cure" Patients remained symptom-free, with negative cultures, 30 days or more post-therapy.
Complete symptomatic relief — defined as complete relief of vulvar pruritus, burning and irritation, plus...
Complete microbiological success — negative KOH smear and negative NICKERSON'S* Medium Culture...for 30 days or more post-therapy.

Excellent clinical results The excellent clinical results with MONISTAT Cream suggest that it should be "...an effective agent for the treatment of vulvovaginal candidiasis in...particularly challenging cases (antibiotic users, diabetics, and the debilitated) as well as in the majority of routine candidal infections."[1]

†MONISTAT Cream may be used in second and third trimester patients. However, in first trimester patients, it should be used only when the physician considers it essential to the welfare of the patient. Please see Precautions in prescribing information.

1. Davis, J.E. et al.: Comparative evaluation of MONISTAT and Mycostatin in the treatment of vulvovaginal candidiasis, *Obstet Gynecol* 44:403 (Sept) 1974.

The one to initiate therapy with —

MONISTAT Cream
TRADEMARK
(MICONAZOLE NITRATE 2%)

Prescribing information
Description: MONISTAT (miconazole nitrate 2%) is a water-miscible, white cream containing as the active ingredient, 2% miconazole nitrate, 1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy) phenethyl] imidazole nitrate.
Actions: MONISTAT Cream exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown.
Indications: MONISTAT Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As MONISTAT Cream is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis*) should be ruled out by appropriate laboratory methods.
MONISTAT is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See PRECAUTIONS.)

*TRADEMARK

Contraindication: Patients known to be hypersensitive to this drug.
Precautions: GENERAL: Discontinue drug if sensitization or irritation is reported during use.
LABORATORY TESTS: If there is a lack of response to MONISTAT, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens.
PREGNANCY: MONISTAT Cream was used in 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women.
Since MONISTAT Cream is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient.
Adverse reactions: Thirty-nine (7.4%) of the 528 patients treated with MONISTAT reported complaints during therapy that were possibly drug-related. Most complaints were reported during the first week of therapy. Vulvovaginal burning, itching or irritation occurred in 6.6%, while other complaints such as vaginal burning, pelvic cramps, hives, skin rash and headache occurred rarely (each less than 0.2% patient incidence). The therapy-related dropout rate was 0.9%.
Dosage and administration: One applicatorful is administered intravaginally once daily at bedtime for 14 days. Course of therapy may be repeated after other pathogens have been ruled out by appropriate smears and cultures.
Supplied: MONISTAT Cream is available in 3 oz. (85 g) tubes with Ortho* Measured-Dose Applicator.
MONISTAT (miconazole nitrate 2%) is a development of Ortho Pharmaceutical Corporation and Janssen Pharmaceutica, Belgium. OJ 690-5

Ortho

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Articles to appear in early issues

Fertility in women with gonadal dysgenesis
F. I. Reyes, M.D., K. S. Koh, M.D., B.S., and C. Faiman, M.D., M.Sc.
Winnipeg, Manitoba, Canada

Amylases of the genital tract. I. Isoamylases of genital tract tissue homogenates and peritoneal fluid
G. Skude, P.-A. Mårdh, and L. Weström
Malmö and Lund, Sweden

Immunologic studies in patients with trophoblastic neoplasia
Yutaka Tomoda, M.D., Masakazu Fuma, M.D., Norihiko Saiki, M.D., Naotaka Ishizuka, M.D., and Tatsuya Akaza
Nagoya, Japan

Nonstressed fetal heart rate monitoring in the antepartum period
France Rochard, M.D., Barry S. Schifrin, M.D., Francoise Goupil, M.D., Helene Legrand, M.D., Josette Blottiere, M.D., and Claude Sureau, M.D.
Paris, France, and Boston, Massachusetts

Screening for detecting twin pregnancy
Madis Mägiste, M.D., Henning von Schenk, M.D., Nils-Otto Sjöberg, M.D., Ph.D., Jan Thorell, M.D., Ph.D., and Anders Åberg, M.D.
Lund, Sweden

Uterine activity in the multiparous patient
James R. Huey, Jr., Lieutenant Colonel, USAF, MC, Alexander Al-Hadjiev, M.D., and Richard H. Paul, M.D.
Los Angeles, California

Untreated endocervical gonorrhea and endometritis following elective abortion
Ronald T. Burkman, M.D., James A. Tonascia, Ph.D., Milagros F. Atienza, M.D., and Theodore M. King, M.D., Ph.D.
Baltimore, Maryland

Scalp abscess: A complication of the spiral fetal electrode
Craig A. Winkel, M.D., Donald L. Snyder, M.D., and John B. Schlaerth, M.D.
San Francisco, California

Metabolites of meperidine in the fetal and maternal serum
J. C. Morrison, M.D., F.A.C.O.G., W. D. Whybrew, M.S., S. I. Rosser, M.D., E. T. Bucovaz, Ph.D., W. L. Wiser, M.D., F.A.C.O.G., and S. A. Fish, M.D., F.A.C.O.G.
Memphis, Tennessee

Changing Your Address . . .

WHEN YOU MOVE, PLEASE:

(1) Notify us to change your address—allow us six weeks to make the change.

(2) Mention the name of this Journal. (We publish thirteen periodicals).

(3) Give us your old address. If possible, return the addressed portion of the envelope in which we sent your last copy.

(4) Give us your new address—complete — including the Zip code number.

(5) Please print your name and address.

Thank You!

CIRCULATION DEPARTMENT
The C. V. Mosby Company
11830 Westline Industrial Dr.
St. Louis, Mo. 63141

OB-GYN, BOARD CERTIFIED OR ELIGIBLE:

Want the advantages of living in a smaller midwestern city free of today's urban problems? But with a growing medical community that rivals that of many bigger cities! Then, consider Aberdeen, South Dakota. Hospital is currently involved in extensive remodeling of OB-Nursery area. Established OB-GYN is willing to share call with newcomer, 2 young, board certified pediatricians with recent neonatal training are anxious to have perinatal colleague join staff. If interested, phone collect: Drs. Dick Mestrich or Randy Heisinger, (605) 229-4407, days or evening, or Mr. Dean Driscoll, St. Luke's Hospital, (605) 225-5110 during the day.

Community Hospital will sponsor first year of private, solo practice for OB-GYN. Prefer someone finishing Residency in June, 1977. Guaranteed income, paid move, malpractice insurance paid and rent-free office and equipment. Please include C. V. Reply Box AJOG-3.

Looking at the unborn.



Ultrasound has become the eyes of OB/GYN. icker Echoview® systems with EDC™ have dded vision to those eyes with the first reamlined, user-designed ultrasound ystem — Echoview System 80L.

System 80L is easy to use. Control anels are placed adjacent ppropriate display panels. ndividual controls have an uthoritative "feel," are gically grouped and are rranged to assure a inimum of hand and rm fatigue.

The remote hand ontrol lets the oper- tor stay next to the atient to concen- ate on scanning.

Plus, System 80L flexible enough be innovative. or example, when icker developed DC, now a syn- nym for gray scale, e made sure it was eld-retrofittable to arlier, exclusively istable systems. The me is true with future finements.

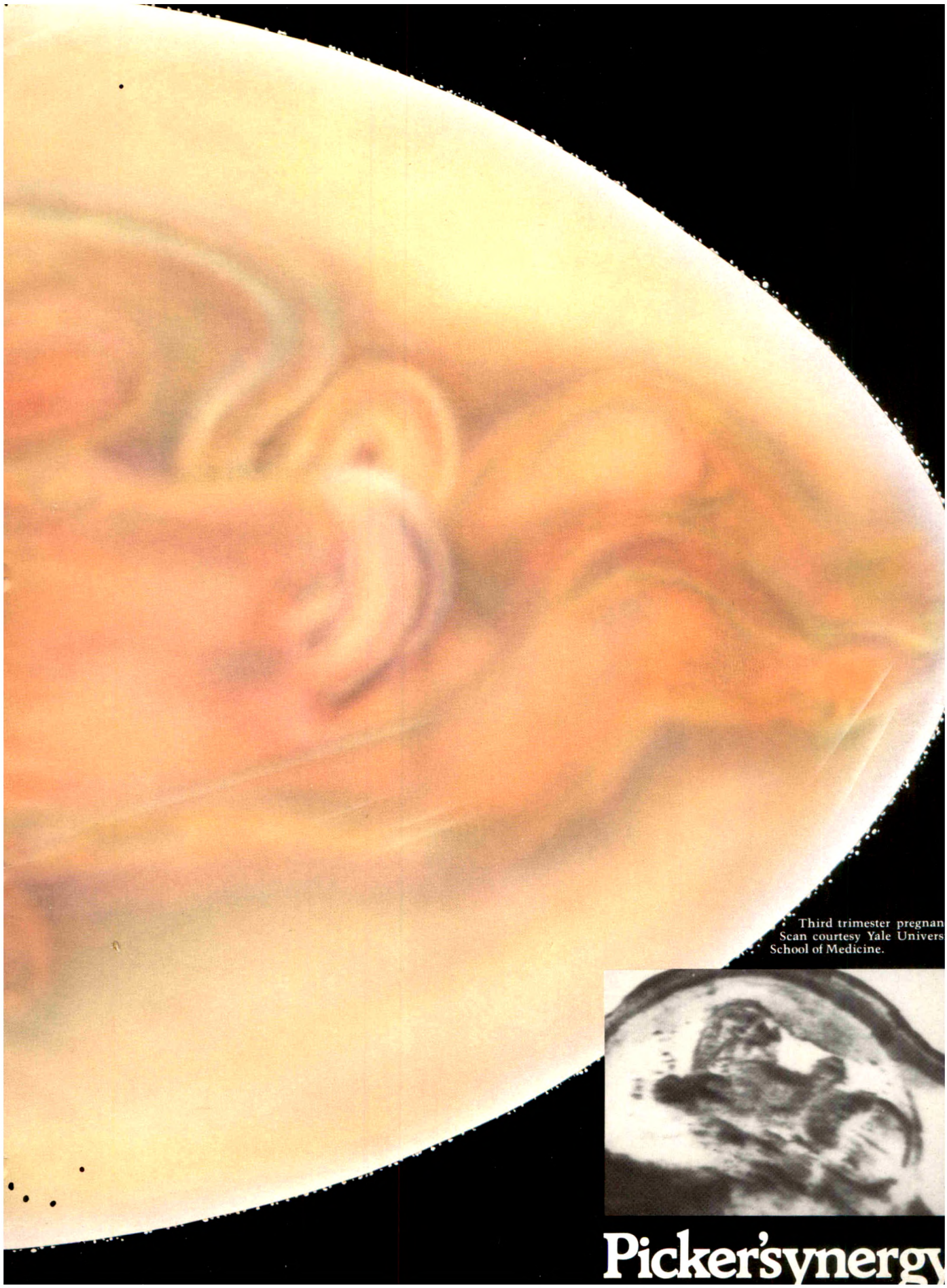
That is what we mean by ickersynergy — the complete nterfacing of systems and rvices for improved diagnostic isualization.

To look at the future of ultrasound OB/GYN, look to the Echoview ystem 80L.

Talk to your Picker representative. Or rite Picker Corporation, 12 Clintonville oad, Northford, CT 06472.

PICKER®

ONE OF THE GIT COMPANIES

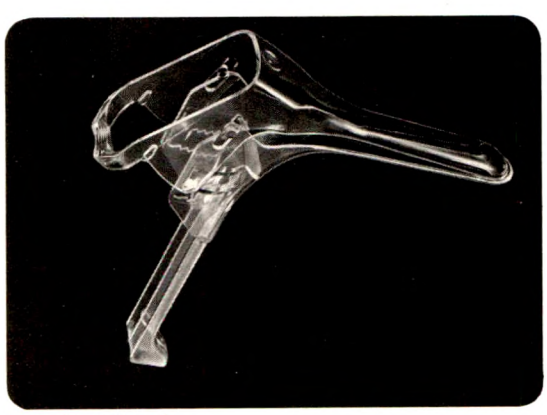


Third trimester pregnan
Scan courtesy Yale Univers
School of Medicine.

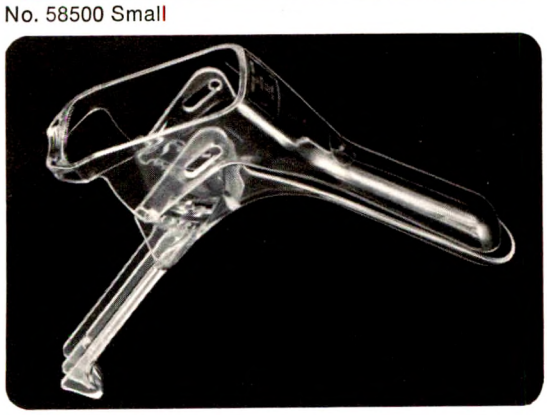
Picker'synergy



PRE-LUBRICATED disposable vaginal specula...now in two sizes.



No. 58500 Small



No. 58501 Regular

Just wet the new Welch Allyn KleenSpec® Pre-Lubricated Disposable Vaginal Specula with water—and they're ready for use!

Check these advantages:

- ☐ Compatible with Pap Smear procedures
- ☐ Easier insertion—minimizes trauma
- ☐ Speeds examinations—saves time
- ☐ No cleanup as with ordinary lubricants
- ☐ New small size specula have same advantages as the regular size
- ☐ Individually packaged—assures cleanliness and prevents cross-contamination
- ☐ One-hand operation—elevation plus angulation
- ☐ Built-in mucus barrier
- ☐ Optional fiber optic illuminator No. 78500

Contact your Authorized Welch Allyn Distributor TODAY

WELCH ALLYN®

WELCH ALLYN, INC. Skaneateles Falls, N. Y. 13153 U.S.A

OBSTETRICS

Blood as a potential vehicle for the cytomegaloviruses

GILLES R. G. MONIF, M.D.
GEORGE I. DAICOFF, M.D.
LYNN L. FLORY, M.D.
Gainesville, Florida

This study analyzed transfused blood as a potential vehicle for infectious cytomegalovirus (CMV) particles. A total of 207 patients who received a total number of 897 units of blood were monitored. A complement-fixing antibody titer of 1:8, as determined by micro-titer technique, was observed in 14.8 per cent of the blood units. A total of 140 individuals in this study were serosusceptible. Eighty-six serosusceptible individuals did not receive blood containing complement-fixing CMV antibodies. In this patient population three instances of seroconversion were identified. Among the 54 serosusceptible individuals who received at least one unit of blood whose complement-fixing titer to the AD-169 strain of CMV was 1:8 or greater, 13 seroconversions were observed.

THE CYTOMEGALOVIRUSES are among the major viral teratogens; their long evolution paralleled to that of man has been such that they have penetrated and utilized every conventional mode of dissemination.[1] As well as the normal hand-to-mouth type of dissemination characteristics of the herpes group of viruses, the spread of the CMV's may occur by semen from the individuals harboring the virus as well as through the breast milk of infected women.[2, 3] To the list of biologic fluids capable of potentially harboring the virus, blood must now be added. Experience with extracorporeal circulation and allotransplantation has provided provocative evidence which suggests that a certain number of donors experience prolonged viremia.[4–7] If blood from such an individual is transfused into a susceptible patient, a spectrum ranging from subclinical infection to the posttransfusion syndrome may be observed.[8–12] Were such a patient to be pregnant, the probability of fetal involvement would be great.[1, 3]

This study attempted to analyze blood as a potential vehicle for CMV dissemination in terms of the possibility of identifying those units which may harbor infectious CMV particles.

Materials and methods

Study population. The patient population was drawn from three sources: (1) pediatric patients undergoing primarily cardiovascular surgery; (2) women of childbearing age requiring transfusion either as a complication associated with parturition or as a consequence of gynecologic procedure; and (3) an older, postmenopausal female population constituted of women on the gynecologic oncology service at the Shand's Teaching Hospital. Patients with malignancies of the lymphoreticulum system or patients receiving immunosuppressive therapy or chemotherapy were excluded from the study population.

Antibody determinations. The sera for serologic

From the Section of Infectious Diseases, Department of Obstetrics and Gynecology, Department of Pathology and Department of Surgery, University of Florida College of Medicine.

This study was supported in part by National Institutes of Health Grant No. HL-14266.

Received for publication August 1, 1975.

Revised March 11, 1976.

Accepted March 18, 1976.

Reprint requests: Gilles R. G. Monif, M.D., Depart. of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida 32610.

Table I. Profile of serosusceptible blood recipient developing evidence of CMV infection following transfusions

No.	*No. of units transfused*	*No. of units with antibody AD-169 titer*	*Maximum titer*	*Duration of storage of each unit with antibody titer (days)*	*Changes in antibody AD-169 titer*
1	2	1	1:8	10	<1:4 to 1:16—1:32
2	2	2	1:8 1:32	19,20	<1:4 to 1:32
3	9	2	1:8 1:8	1,11	<1:4 to 1:16—1:32
4	11	3	1:8 1:8 1:8	4,7,9	<1:4 to 1:16—1:32
5	17	3	1:8 1:16 1:16	17,17,17	<1:4 to 1:16
6	2	1	1:16	1	<1:4 to 1:64
7	17	1	1:16	9	<1:4 to 1:32
8	4	1	1:8	5	<1:4 to 1:16
9	9	2	1:8 1:16	4,4	<1:4 to 1:16—1:32
10	8	2	1:16 1:32	0,1	<1:4 to 1:32
11	15	1	1:64	8	<1:4 to 1:16—1:32
12	6	1	1:8	7	<1:4 to 1:32
13	6	2	1:8 1:8	2,2	<1:4 to 1:16—1:32
1	4	0	<1:4	N.A.*	<1:4 to 1:64
2	4	0	<1:4	N.A.	<1:4 to 1:16
3	4	0	<1:4	N.A.	<1:4 to 1:64

*N.A. = Not available.

Table II. Tabular summary of consequences of transfusion of blood with or without anti-CMV into recipients with or without serological evidence of humoral immunity

	No. of recipients transfused with seronegative blood and No. of seroconversions	*No. of recipients transfused with seronegative blood and No. of seroconversions*
Susceptible recipients	86/3 (3.4% incidence rate)*	54/13 (24.1% incidence rate)*
Seropositive recipients	43/0	24/3

*The corrected chi-square value ($P < 0.005$).

testing for the presence or absence of complement-fixing antibodies included: (1) pretransfusion serum specimens, (2) aliquots from each blood unit utilized, and (3) one or more posttransfusional specimens obtained from 4 to 12 weeks following the operative procedure (average 59 days). All of the specimens were titrated simultaneously in the same test and in duplicate for the presence or absence of complement-fixing antibodies to the CMV infection with the micro-titer technique.[14] A single lot of AD-169 CMV antigen obtained from Flow Laboratories was utilized in the study. Seroconversion indicative of infection was interpreted as a *greater* than fourfold increase in titer. The validity of the titer obtained in instances of seroconversion were confirmed in at least one additional test with a second lot of antigen. The specificity of seroconversion was confirmed qualitatively, but not quantitatively, with the commercial modification of Hanshaw's indirect immunofluorescent technique for the CMV's with an anti-IgG conjugate (available through Electro-Nucleonics Laboratory, Inc.).[15]

Results

Of the 391 patients monitored, 207 became the study population by virtue of completeness of specimen collection. In the 897 units of blood transferred into the 207 recipients, a complement-fixing antibody titer of 1:8 or greater (as determined by micro-titer technique) was observed in 14.8 per cent. If the minimal threshold titer was decreased to 1:4 or greater, an incidence of 18.5 per cent seropositivity was identified.

A total of 140 individuals in this study did not have serum antibodies and were hence susceptible. Fifty-

four of these serosusceptible patients received at least one unit of blood whose complement-fixing titer to the AD-169 strain was 1:8 or greater and in 13 of the 54, seroconversion was demonstrated. The remaining 86 serosusceptible individuals were transfused with blood which did not contain the complement-fixing CMV antibodies, and in these, three instances of seroconversion were identified (Table I).

There were 67 patients with pre-existing titers. No evidence of amnestic response was observed in 43 of these patients who received seronegative blood, whereas, three of 24 recipients transfused with seropositive blood responded with a four-fold rise in titer (Table II).

If one restricted serologic observations only to the seven serosusceptible individuals receiving a unit of blood with a titer of high anti-CMV (1:32 or greater), two seroconverted, two experienced a fourfold rise, and three individuals had no evidence of infection observed. In the six individuals with pre-existing titer, three had an antibody titer greater than or equal to 1:64; in the remaining three individuals a fourfold rise was observed. Among the remaining 18 seropositive individuals receiving at least one unit of blood containing an antibody titer of 1:16 or less, no individual exhibited a fourfold or greater rise. The average duration of storage time was 8.9 days of a blood unit containing a 1:8 or greater titer of antibody AD-169 cytomegalovirus transfused into a susceptible individual who then seroconverted. The average storage time for those seropositive units which were transfused into susceptible recipients who did not develop serologic evidence of infection was 11.9 days.

Comment

The premise being explored in this paper was that by the exclusion of seropositive units of blood to a recipient, transfusion CMV infection might be avoided. The exclusion of seropositive blood, although statistically reducing the probability ($P < 0.0005$), did not invariably preclude the possibility of acquiring the CMV infection. Three of the 86 susceptible recipients transfused with seronegative blood did develop significant titers to the CMV's indicative of infection. These cases would either be a reflection of the widespread endemicity of the CMV's (particularly within the hospital environment) or the failure of the threshold sensitivities of the testing system to identify units with low titers of CMV antibodies.

The absence of an absolute correlation between blood-containing CMV antibodies and subsequent acquisition of infection is not surprising in view of the antigenic heterogeneity of the CMV's. The AD-169 strain of CMV's is used in normal serologic testing because it affords the broadest antigenic spectrum. Though poorly characterized, the CMV's carry the reputed strain designations of the Ribardiere Heermange, Kerr, AD-169, Hammond, and Davis.[16] Titers to heterologous strains would obviously be less because of only partial sharing of the antigenic determinants. If one attempts to restrict observations to only high titers (1:32 or greater), the correlation with the probability of infection is enhanced.

Similarly, no adequate explanation was identified to explain why certain units with high titers presumably possess cell-associated virus and others do not.

What the study suggests is that blood is a potential vehicle for infectious CMV particles and that exclusion of seropositive donors can reduce the probability of ensuring CMV infection significantly. However, the inability to differentiate heterologous from homologous antibody presents a real problem in terms of eliminating blood units potentially harboring infectious CMV virions.

Transfusion CMV infection is usually not associated with adverse host sequelae, unless the recipient is: (1) undergoing homograph transplantation and receiving suppressant therapy or (2) pregnant. If a gravida with no antibodies to the CMV's requires a transfusion in gestation, it is best that it be done with units of blood containing no detectable antibody titer to the CMV.

The authors wish to thank Dr. Gerald L. Schiebler, Professor and Chairman of the Department of Pediatrics and Dr. Ira H. Gessner, Professor of Pediatrics. Statistical analysis was performed by Ronald Marks, Ph.D., Department of Statistics.

REFERENCES

1. Weller, T. H.: The cytomegaloviruses: Ubiquitous agents with protean clinical manifestations, N. Engl. J. Med. **285:** 267, 1971.
2. Lang, D. L., and Kummer, J. R.: Demonstration of cytomegalovirus in semen, N. Engl. J. Med. **287:** 756, 1972.
3. Hayes, K., Danks, D. M., Gibas, H., and Ion, J.: Cytomegalovirus in human milk, N. Engl. J. Med. **287:** 177, 1972.
4. Craighead, J. E., Hanshaw, J. B., and Carpenter, C. B.: Cytomegalovirus infection after renal allotransplantation, J. A. M. A. **201:** 725, 1967.
5. Lang, D. J., and Hanshaw, J. B.: Cytomegalovirus infection and the postperfusion syndrome. Recognition of primary infection in four patients, N. Engl. J. Med. **280:** 1145, 1969.
6. Rifkind, D., Goodman, N., and Hill, B. B., Jr.: The clinical significance of cytomegalovirus infection in renal transplant recipients, Ann. Intern. Med. **66:** 1116, 1967.

7. Henle, W., Henle, G., Scriba, M., et al.: Antibody responses to the Epstein-Barr virus and cytomegalovirus after open-heart surgery, N. Engl. J. Med. **282:** 1068, 1970.
8. Diosi, P., Moldovan, E., and Tomescu, N.: Latent cytomegalovirus infection in blood donors, Br. Med. J. **4:** 660, 1969.
9. Foster, K. M., and Jack, I.: A prospective study of the role of cytomegalovirus in post-transfusion mononucleosis, N. Engl. J. Med. **280:** 1311, 1969.
10. Prince, A. M., Szmuness, W., Million, S. J., and David, D. S.: A serologic study of cytomegalovirus infections associated with blood transfusion, N. Engl. J. Med. **284:** 1125, 1971.
11. Klemola, E., and Kääriänen, L.: Cytomegalovirus as a possible cause of a disease resembling infectious mononucleosis, Br. Med. J. **2:** 1099, 1965.
12. Henson, D.: Cytomegalovirus inclusion disease following multiple blood transfusions, J. A. M. A. **199:** 278, 1967.
13 Monif, G. R. G.: Viruses as teratogens, Clin. Obstet. Gynecol. **18:** 209, 1975.
14. Sever, J. L.: Application of a microtechnique to viral serological investigations, J. Immunol. **88:** 320, 1962.
15. Hanshaw, J. B., Steinfeld, H. J., and White, C. J.: Fluorescent antibody test for cytomegalovirus microglobulin, N. Engl. J. Med. **279:** 566, 1968.
16. Weller, T. H., Macaulay, J. C., Craig, J. M., et al.: Isolation of intranuclear inclusion producing agents from infants with illnesses resembling cytomegalic inclusion disease, Proc. Soc. Exp. Biol. Med. **94:** 4, 1957.

The management of the pregnant patient with idiopathic thrombocytopenic purpura

JAMES M. MURRAY, M.D., MAJOR, USAF, MC
ROBERT E. HARRIS, M.D. PH.D., LIEUTENANT COLONEL, USAF, MC
Lackland Air Force Base, Texas

The approach to management of idiopathic thrombocytopenic purpura (ITP) during pregnancy remains controversial—particularly regarding the method of delivery. Regardless of the maternal platelet count, we believe that these patients should be delivered by elective cesarean section at term because of the continued presence of maternal antiplatelet IgG antibodies, which cross the placenta. Despite the method of treatment used to increase maternal platelets, immunologic factors are significant for neonatal involvement and should be considered in the management of these patients. The single largest factor responsible for reported neonatal losses has been intracranial hemorrhage secondary to thrombocytopenia and birth injury. Two patients with ITP are presented with data to substantiate our position on the method of delivery. The infants were transiently thrombocytopenic following delivery (despite adequate maternal levels of platelets).

IDIOPATHIC thrombocytopenic purpura (ITP), the most common form of thrombocytopenia,[1] is a disease of accelerated platelet destruction. This diagnosis is generally made by a process of elimination of other factors which can cause a decreased platelet count, such as drugs, infection, or transfusions. Most hematologists require that normal or increased numbers of megakaryocytes be demonstrated on bone marrow examination before the diagnosis is made. ITP has a predilection for young females.[2] Thus the obstetrician may be involved in the management of ITP patients during pregnancy. A rational approach to the obstetric management of the ITP patient is presented, based upon literature review, practical immunology, and our experience with two patients at Wilford Hall USAF Medical Center.

From the Department of Obstetrics and Gynecology, Wilford Hall USAF Medical Center.

The opinions expressed in this manuscript are those of the authors and not necessarily those of the United States Air Force nor the Department of Defense.

Received for publication December 8, 1975.

Revised March 17, 1976.

Accepted March 19, 1976.

Reprint requests: Dr. James M. Murray, 12710 Braewood Glen Lane, Houston, Texas 77072.

Patient reports

Patient 1. D. L., a 19-year-old woman, presented at 17 weeks' gestation with profuse gingival bleeding following dental prophylaxis. Normal PT, PTT, and fibrinogen were obtained on coagulation evaluation, but only 8,000 platelets per cubic millimeter were present. Normal numbers of megakaryocytes were present on bone marrow biopsy and aspiration. She had no intercurrent infectious diseases and was not using any medications. Upon physical examination, scattered purpuric lesions were noted over the lower extremities. The gingival bleeding was stopped with local treatment and she was begun on 100 mg. of Prednisone per day. Over the next 5 days, the platelet count rose to 105,000 per cubic millimeter. She was maintained on this glucocorticoid dosage until 28 weeks' gestation, when slow tapering of the dosage was begun, with the platelet counts remaining normal. At 34 weeks' gestation the membranes ruptured spontaneously and she was delivered by cesarean section. Splenectomy was performed concomitantly. The infant's platelet count at birth was 136,000 per cubic millimeter, but rapidly fell to 40,000 per cubic millimeter during the first 4 hours of life. The platelet count slowly rose thereafter and has remained normal. The infant had no evidence of bleeding. The patient's platelet counts remained normal postoperatively and her steroids were discontinued.

Patient 2. L. T., a 21-year-old woman, was initially

seen at 36 weeks' gestation. At age 12 she had developed a clinical syndrome with purpura and excessive bleeding from minor trauma. Full diagnostic evaluation at that time was compatible with a diagnosis of ITP. She was treated by splenectomy, with resolution of purpura and abnormal bleeding. During this pregnancy she had no bleeding or purpura and platelet counts ranged from 250,000 to 490,000 per cubic millimeter. At 39 weeks' gestation she was delivered by elective cesarean section without complications. The infant's platelet count was 40,000 per cubic millimeter at birth, remained below 100,000 per cubic millimeter for the first 4 days of life, and thereafter slowly rose to normal levels. There was no evidence of infant bleeding.

Comment

In normal hemostasis the role of the platelet begins shortly after any injury to a blood vessel. The initial step is platelet adhesion and aggregation, followed by the release of numerous factors—mainly phospholipids—from the platelets, which act at various stages in the coagulation cascade to achieve control of bleeding. The platelet also plays a role, as yet undetermined, in the phenomenon of clot retraction. Thus interference with the normal function or number of platelets will result in bleeding disorders.

There is convincing—but largely indirect—evidence that the pathogenesis of ITP is immunologic. Serum from ITP patients contains a species-specific "factor" which can be adsorbed with normal platelets and is measured in the IgG fraction of the serum. When this factor is infused into normal subjects, some show a fall in platelet counts.[3] However, there are no reliable tests available at the present time to detect this antibody. Splenic sequestration of antibody-coated platelets with subsequent phagocytosis of the platelets is well accepted as the mechanism of thrombocytopenia in ITP.[4] The initiating factor for development of antiplatelet antibodies is unknown, but some evidence suggests an autoimmune phenomenon.[3] The initial treatment of ITP, with or without associated pregnancy, has been primarily with corticosteroids. When steroid therapy has failed, or if exacerbation occurs after successful treatment, then splenectomy is performed, usually with resultant long-term correction of the thrombocytopenia.

The obstetrician may be involved in the management of patients with ITP as this disease has a predilection for females in the childbearing age group. The patient may initially present with the disease during pregnancy or a patient in remission may relapse. The maternal mortality rate associated with ITP has been reported to be as high as 11 per cent, especially in that group of patients whose thrombocytopenia antedated pregnancy and who were untreated during pregnancy.[5, 6] Most of the deaths and serious bleeding problems were related to incisions or lacerations and only rarely to uterine bleeding, where hemostasis is largely mechanical. With the availability of platelet transfusions for surgery, this maternal mortality rate has been significantly reduced.[5, 6]

The newborn infant with thrombocytopenia from any cause is subject to an increased risk from bleeding, especially at delivery, in the form of intracranial hemorrhage. The perinatal mortality rate has been reported to be 12.7 to 21 per cent.[7, 8] Mendel and Sparkman[9] reported a perinatal mortality rate of 19 per cent in 79 pregnancies associated with maternal ITP.

The mechanism of neonatal thrombocytopenia, secondary to maternal ITP, is placental transfer of antiplatelet IgG. In mothers with thrombocytopenia at the time of delivery, fetal thrombocytopenia ranges from 50 to 73 per cent.[8, 9] Definition of neonatal thrombocytopenia has been variable, but a platelet count of less than 50,000 per cubic millimeter warrants great concern over bleeding. This figure may be too low because once bleeding begins in these infants, the platelet count may fall rapidly with a resultant worsening of the problem.[10]

Infants of thrombocytopenic mothers may therefore be best delivered by cesarean section to reduce birth trauma related to passage through the bony pelvis.[11] The patients whose platelet counts are normal at the time of delivery have generally been allowed to deliver vaginally on the presumption that these fetuses would have normal platelet counts. The literature does not support this position. Mendel and Sparkman,[9] in a review of 40 patients who had undergone splenectomy for ITP prior to pregnancy, found that 31 of the infants (77.5 per cent) were thrombocytopenic at birth. Of these 40 patients, 15 had normal platelet counts at delivery and six (40 per cent) had infants with thrombocytopenia at birth. Slaughter and associates[12] reviewed cases of ITP with special reference to splenectomy and found no differences in the incidence of thrombocytopenia in the neonate; the maternal platelet count at delivery was not available in many instances. Tancer[13] reported 21 patients with normal platelet counts who had undergone splenectomy for ITP prior to pregnancy. One infant died of intracranial bleeding, three infants had purpuric manifestations, and two other infants had thrombocytopenia without purpura. Thus Tancer concluded that

neonatal purpura may occur regardless of prior therapy and in the presence of a normal maternal platelet count. Heys[14] reported 38 similar patients with a perinatal mortality rate of 17 per cent, with three of the neonatal deaths being secondary to intracranial hemorrhage. Of 29 other infants for whom records were available, six (18 per cent) had purpura and three (9 per cent) had thrombocytopenia without purpura. The over-all incidence of infant bleeding problems was 37 per cent. Heys concluded that all infants born to mothers with ITP must be considered at risk for thrombocytopenia and evaluated carefully in the neonatal period. Anthony and Krivit[15] noted that a woman with ITP in remission may continue to produce purpuric infants and that if bleeding was avoided, the disease in the neonate was benign and self-limited. Territo and associates[11] felt justified in separating pregnant women with ITP into two categories at delivery: (1) mothers with platelet counts less than 100,000 per cubic millimeter and (2) mothers with platelet counts greater than 100,000 per cubic millimeter. Cesarean section was advocated for the first group because they found that 27 of the 31 pregnancies (87 per cent) resulted in thrombocytopenic infants. Mothers in the second group would be allowed to deliver vaginally because of the decreased risk of neonatal thrombocytopenia. However, six of 22 infants (27 per cent) born to mothers in the second group had platelet counts less than 100,000 per cubic millimeter. Though the incidence of thrombocytopenic infants born to mothers in the second group was lower, we do not feel this incidence to be acceptable.

Conclusion

The treatment and correction of maternal ITP do not affect the continuing presence of the circulating antiplatelet factor, which is transmitted freely across the placenta. There are no available means to predict those infants who will have thrombocytopenia at birth. The infant mortality rate with thrombocytopenia is very high, especially as this is a benign, self-limited condition. Many of the infant deaths are related to birth trauma, especially intracerebral bleeding.

We conclude and recommend that infants born to mothers with ITP, whether symptomatic or in remission at the time of delivery, should not be subjected to the trauma of vaginal delivery but rather should be delivered by cesarean section.

The argument that thrombocytopenic mothers should not be subjected to cesarean section because of the risks of bleeding is no longer compelling. Due to the availability and efficacy of platelet transfusions, these patients can be managed in such a way as to prevent excessive bleeding. With the use of a very generous lower uterine segment vertical incision, the infant can be delivered atraumatically. These patients might also have splenectomy done at the time of cesarean section depending upon the circumstances of timing and personnel.

Ultimately, the validity of the recommendations presented here will depend upon a testing of our conclusions over a longer period of time and upon careful reporting of individual cases. However, we consider this management of ITP in pregnancy to be a rational approach in the best interest of these infants.

REFERENCES

1. Wintrobe, M. A.: Clinical Hematology, Philadelphia, 1975, Lea & Febiger, Publishers, p. 1071.
2. Lozner, E. L.: The thrombocytopenic purpuras, Bull. N. Y. Acad. Med. **30:** 184, 1954.
3. Dixon, R., Rosse, W., and Ebbert, L.: Quantitative determination of antibody in idiopathic thrombocytopenic purpura. Correlation of serum and platelet-bound antibody with clinical response, N. Engl. J. Med. **292:** 230, 1975.
4. Aster, R. H., and Keene, W. R.: Sites of platelet destruction in idiopathic thrombocytopenic purpura, Br. J. Haematol. **16:** 61, 1969.
5. Robson, H. N., and Davidson, L. S. P.: Purpura in pregnancy with special reference to idiopathic thrombocytopenic purpura, Lancet **2:** 164, 1950.
6. Rogers, T. E.: Thrombocytopenia in pregnancy following splenectomy, Am. J. Obstet. Gynecol. **78:** 806, 1959.
7. Pearson, H. A., Shulman, N. R., and Marder, V. J.: Isoimmune neonatal thrombocytopenic purpura; clinical and therapeutic considerations, Blood **23:** 154, 1964.
8. Laros, R. K., and Sweet, R. L.: Management of idiopathic thrombocytopenic purpura during pregnancy, Am. J. Obstet. Gynecol. **122:** 182, 1975.
9. Mendel, E. B., and Sparkman, R.: Idiopathic thrombocytopenic purpura in pregnancy, J. Int. Coll. Surg. **28:** 156, 1957.
10. DeLemos, R.: Personal communication.
11. Territo, M., Finkelstein, J., and Oh, W.: Management of autoimmune thrombocytopenia in pregnancy and in the neonate, Obstet. Gynecol. **41:** 579, 1973.
12. Slaughter, D. P., et al.: Surgical treatment of ITP in pregnancy, Arch. Surg. **63:** 132, 1951.
13. Tancer, M. L.: Idiopathic thrombocytopenic purpura and pregnancy: Report of five new cases and review of the literature, Am. J. Obstet. Gynecol. **79:** 148, 1960.
14. Heys, R. F.: Childbearing and idiopathic thrombocytopenic purpura, J. Obstet. Gynaecol. Br. Commonw. **73:** 205, 1966.
15. Anthony, B., and Krivit, W.: Neonatal thrombocytopenic purpura, Pediatrics **30:** 776, 1962.

Thrombotic thrombocytopenic purpura associated with pregnancy

HARRY V. MAY, JR., M.D.
GUY M. HARBERT, JR., M.D.
W. NORMAN THORNTON, JR., M.D.
Charlottesville, Virginia

Thrombotic thrombocytopenic purpura (TTP), a disorder of unknown etiology, appears to be a syndrome often associated with infectious, vascular, or autoimmune diseases. When it occurs in pregnancy, TTP can mimic other gestational complications. Two patients with TTP associated with pregnancy form the basis of this report. One patient is the second person known to have survived longer than 2 years after concurrent TTP and pregnancy. This patient had underlying glomerulonephritis and was treated with corticosteroids and heparin. The other patient, in whom an underlying disease process was not identified, was treated unsuccessfully with most of the recommended therapeutic modalities. Patients with concurrent TTP and pregnancy have the same prognosis as nonpregnant patients with TTP. Both groups have a prolonged survival rate of only 10 per cent. Primary treatment should consist of corticosteroids and inhibitors of platelet aggregation. If a rapid response does not occur, splenectomy is indicated. Care must be taken to recognize the pregnancy complicated by TTP, a circumstance which appears to occur more frequently than past reports have indicated.

SINCE Libman first recognized thrombotic thrombocytopenic purpura (TTP) as a distinct entity,[1] approximately 350 cases have been reported.[2] The disorder is of unknown etiology and often follows prodromal upper respiratory or gastrointestinal symptoms. Three features: microangiopathic hemolytic anemia, thrombocytopenia, and transient neurologic abnormalities are seen. Renal disease and fever are also frequently encountered. The diagnosis is confirmed by histologic demonstration of typical lesions in the terminal arterioles and capillaries. Various therapeutic modalities have been used including: inhibitors of platelet aggregation, splenectomy, corticosteroids, heparin, exchange transfusion, and dialysis. The clinical course is rapid, leading to a fatal outcome in most cases. In only approximately 10 per cent of patients is prolonged survival reported.[3]

The two pregnant patients in this report and another reported elsewhere[4] have been treated since 1969 at the University of Virginia Hospital. These three patients represent 11 per cent of all reported cases of TTP associated with pregnancy. This fact has led to the conclusion that TTP occurs more often as a complication of pregnancy than past reports have indicated. The purpose of this report is to familiarize the clinician with TTP so that the differential diagnosis from other obstetric complications can be made and proper therapy instituted.

From the Department of Obstetrics and Gynecology, University of Virginia School of Medicine.

Received for publication December 10, 1975.

Accepted March 9, 1976.

Reprint requests: Guy M. Harbert, Jr., M.D., University of Virginia Hospital, Box 179, Charlottesville, Virginia 22901.

Case reports

Case 1. The patient, a 17-year-old primigravida, was first seen on February 27, 1972, at 28 weeks' gestation. She presented shortly after suffering three grand mal seizures. Her prenatal course had been uneventful except for frontal headaches, which had begun 2 days previously.

Physical examination revealed a young black woman who appeared postictal. The blood pressure was 210/150 mm. Hg; the pulse was 120; the respiratory rate was 28; the temperature was 37° C. Petechiae were present on the neck and extremities. The funduscopic examination was normal. The uterine fundus was 26 cm. above the symphysis and fetal heart tones were audible. The hematocrit was 38 per cent. The white blood count was 25,000 per cubic millimeter, with a

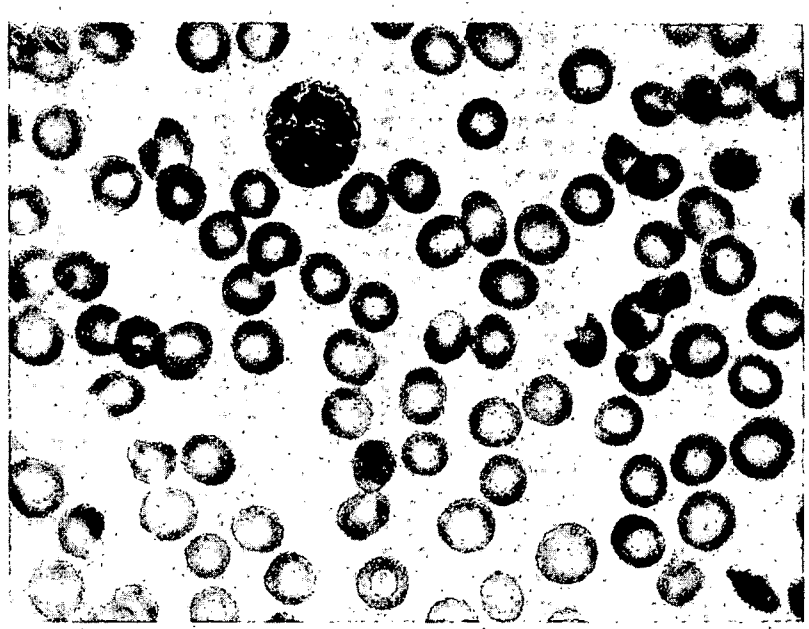


Fig. 1. Peripheral blood smear demonstrating microangiopathic hemolytic anemia. No platelets are present and many bizarre-shaped fragments of red cells are seen. (Wright and Giemsa stain; ×1,500.)

normal differential count, and the reticulocyte count was 6.3 per cent. The peripheral blood smear (Fig. 1) showed many schistocytes, burr cells, and other bizarre forms. Urinalysis revealed: pH 6.3, 3+ albumin, many red blood cells, and a few white blood cells per high-power field. The blood urea nitrogen was 46 mg. per 100 ml.; creatinine, 2.3 mg. per 100 ml.; total bilirubin, 1.0 mg. per 100 ml. (normal, 0.3 to 1.5); lactic dehydrogenase, 600 I.U. (normal, 120 to 230); serum glutamic oxalacetic transaminase, 250 I.U. (normal, < 60). The platelet count was 49,000 per cubic millimeter (normal, 250,000 to 450,000); bleeding time, 14 minutes (normal, 0.5 to 9.5); prothrombin time (PT), 14 seconds (normal, 11 to 15); partial thromboplastin time (PTT), 24 seconds (normal 20 to 29); fibrin degradation products, 12 μg per 100 ml.; fibrinogen, 500 mg. per 100 ml. The direct Coombs' test was negative.

The patient was started on intravenous magnesium sulfate to control the convulsions. Bone marrow aspiration revealed normoblastic erythroid hyperplasia and increased numbers of megakarocytes. The working diagnosis was TTP and the patient was begun on prednisone, 60 mg. every day, and heparin, 5,000 units every 6 hours. Because of falling hematocrit, whole blood replacement was begun. On hospital day 3, the patient became febrile, hypotensive, and oliguric. On the next day the patient spontaneously passed a meconium-stained stillborn infant weighing 1,500 grams. Gradually increasing platelet numbers and improvement in renal and mental status followed.

Renal biopsy (Fig. 2) done on postpartum day 20 revealed focal acute glomerulonephritis and the vascular lesions of TTP. The patient continued to improve and was discharged on hospital day 37. The serum creatinine was 0.8 mg. per 100 ml. and the platelet count was 400,000 per cubic millimeter. The dosage of prednisone was gradually tapered and after 1 year it was discontinued. In 1974 she became pregnant with an intrauterine device (IUD) in place and aborted spontaneously in the first trimester. She is now in her fourth year after the acute episode of TTP. She is doing well with an IUD in place but is still suffering from mild hemolytic anemia.

Case 2. This 19-year-old white woman, gravida 2, para 0, abortus 1, was seen on April 3, 1975, at 20 weeks' gestation. She had begun to bruise easily 6 months prior to admission and had an episode of transient aphasia 3 months later. Severe nausea and vomiting, bleeding from the gums and nose, weakness of the right hand, and expressive aphasia were noted 1 month before admission.

Her physical examination revealed a blood pressure of 110/80 mm. Hg; the pulse was 80; the temperature was 37° C.; the respiratory rate was 16. Funduscopic examination was normal. Petechiae were present on the hands, legs, and soft palate. Neurologic examination revealed a right inferior quadrantic homonymous hemianopsia, right facial and arm weakness, and expressive aphasia. The uterine fundus was 12 cm. above the symphysis and no fetal heart tones were heard on Doppler ultrasound examination. There was no edema and the deep tendon reflexes were normal. The hematocrit was 30 per cent; the white blood count was

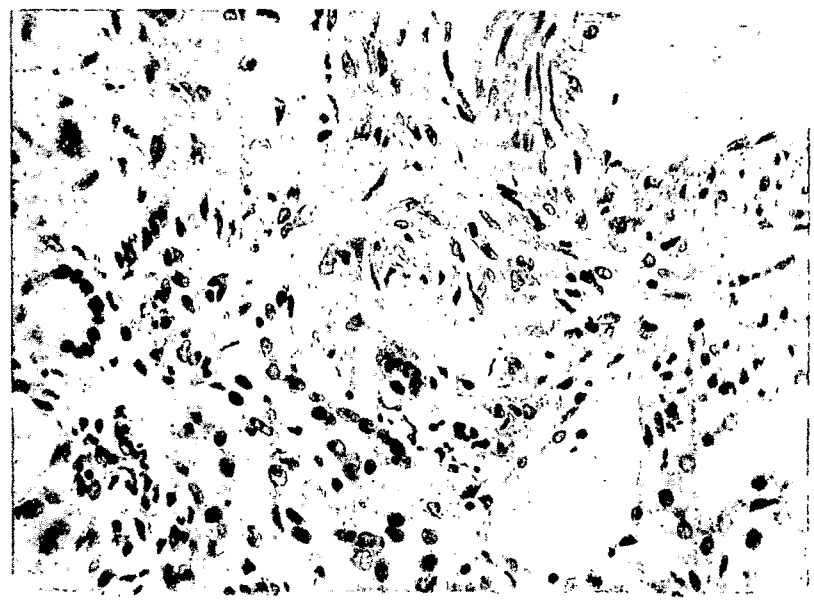


Fig. 2. Kidney biopsy. A small vessel with endothelial proliferation and subendothelial hyaline deposition is present in the center. (Hematoxylin and eosin; ×520.)

9,700 per cubic millimeter, with a normal differential count, and the reticulocyte count was 3.4 per cent. The peripheral blood smear was consistent with microangiopathic hemolytic anemia. Urinalysis revealed: pH. 5.0, 1+ albumin, five red blood cells, and one white blood cell per high-powered field. The blood urea nitrogen was 15 mg. per 100 ml., creatinine 1.0 mg. per 100 ml., total bilirubin 0.5 mg. per 100 ml., lactic dehydrogenase 550 I.U., and serum glutamic oxalacetic transaminase 27 I.U. The direct Coombs' test was negative. Clotting studies included a platelet count of 51,000 per cubic millimeter, fibrinogen 490 mg. per 100 ml., bleeding time 20 minutes, prothrombin time (PT) 13 seconds, partial thromboplastin time (PTT) 21 seconds. Fibrin degradation products were within normal range of 8 μg per 100 ml. Compound B mode sonar examination was consistent with missed abortion. Bone marrow examination was normal. Due to clinical signs suggestive of cerebral vascular accident (CVA), a brain scan was obtained. This revealed decreased flow in the left middle cerebral artery and increased activity of the posterior parietal areas consistent with CVA. The working diagnosis was TTP with fetal death. The patient was started on dipyridamole, 50 mg. every 6 hours, aspirin, 10 gr. every 6 hours, and prednisone, 20 mg. three times a day. These drugs were continued in varying doses during her entire hospital course.

Due to decreasing hematocrit the patient was transfused with two units of packed cells. On hospital day 3, intrauterine prostaglandin injection was performed. The patient failed to abort and underwent dilatation and curettage with removal of an extremely macerated fetus. A gingival biopsy was consistent with thrombotic thrombocytopenic purpura.

By hospital day 7 the patient's platelets had increased to 117,000. Fourteen days later the platelet count had decreased to 60,000 and transient exacerbations characterized her neurologic status. Consequently, with intraoperative platelet transfusion and partial exchange transfusion, the patient underwent total splenectomy. Recent infarcts and vascular lesions of TTP were present in the spleen (Fig. 3). By postoperative day 6 the platelet count had risen to 400,000. With corticosteroid tapering, decreasing platelet count was noted. By postoperative day 21 the platelet count had dropped to 9,000 and cortical blindness was observed. Dextran 70 infusion was given without clinical improvement. An exchange transfusion was performed and vision returned 2 days later, with the platelet count rising to 231,000. On postoperative day 28, high fever and bilateral pleural effusions were noted. Pneumonia was diagnosed and antibiotics were begun. Two days later there was rectal bleeding and increased intracerebral pressure. The hematocrit was 20 per cent, platelet count 198,000, and white blood cells 11,800 per cubic millimeter. On hospital day 54, the patient had cardiopulmonary arrest with unsuccessful attempts at resuscitation. Postmortem examination revealed diffuse vascular lesions diagnostic of TTP.

Comment

The chief clinical manifestations of TTP are purpura, hemorrhage, and transient neurologic abnormalities. Fever, pallor, and hematuria are also frequently noted. In addition to thrombocytopenia, prominent hematologic findings include leukocytosis, reticulocytosis, and microangiopathic hemolytic ane-

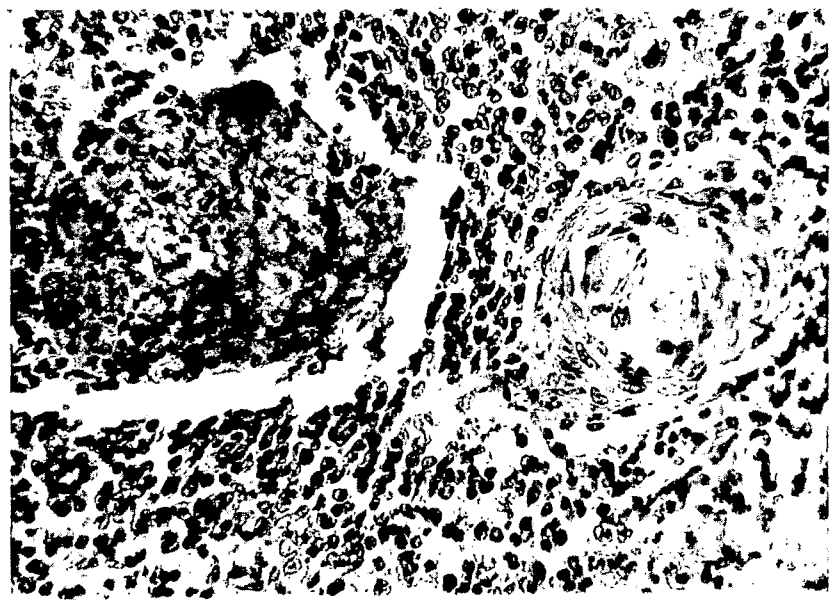


Fig. 3. Spleen. Extensive endothelial proliferation is present on the left side and subendothelial (PAS+) hyaline deposition is present on the right side. (Hematoxylin and eosin; ×625.)

mia (Fig. 1). The direct Coombs' test is negative, as was evidenced by the two patients of this report. Additional confirmation of hemolysis can be demonstrated by the presence of hemosiderin in the urine and decreased haptoglobin levels. The screening test for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and the sickle-cell preparation are both negative. Various tests for immunologic abnormalities are also negative. These include the antinuclear factor (ANF), cryoglobulins, rheumatoid factor, and lupus erythmatosus (LE) preparation. Evidence of mild renal and liver dysfunction is frequently observed. A common histologic feature of TTP is marked vascular endothelial proliferation associated with minimal inflammatory response. The presence of specific vascular lesions in the terminal arterioles and capillaries confirms the diagnosis. These lesions (Figs. 2 and 3) are composed of endothelial fibrin deposits upon which platelets accumulate after endothilial rupture.

Diseases included in the differential diagnosis of TTP are: idiopathic thrombocytopenic purpura (ITP), thrombocytopenia in association with systemic lupus erythematosus, idiopathic autoimmune hemolytic anemia, other "symptomatic" hemolytic anemias, hemolytic uremic syndrome, and acute leukemia. The marked but transient nature of neurologic abnormalities, microangiopathic hemolytic anemia with negative direct Coombs' test, fever, and hematuria with abnormal renal function differentiate TTP from these diseases.

In obstetric patients with thrombocytopenia and fever, septic abortion and other gestationally related infections must be considered in the differential diagnosis. With the inclusion of our two patients, 26 per cent, or seven of the 27 reported cases of TTP associated with pregnancy, have involved seizures. Since eclampsia has been associated with intravascular hemolysis, thrombocytopenia, and other hematologic abnormalities,[5] it must be considered in the differential diagnosis of gestations complicated by TTP. Conversely, TTP should be considered in the differential diagnosis of eclampsia.

The etiology of TTP is unknown. Various infectious agents including meningococci and microtatobiotes have been associated with TTP. Allergic, vascular, and autoimmune diseases have also been incriminated. Others[6] believe that TTP might be one facet of the snydrome of disseminated intravascular coagulation (DIC). However, it has been shown that DIC is a very unusual finding in TTP. The two patients in this report did not have the coagulation profile of DIC. An elevation in fibrin degradation products, previously reported in patients with TTP,[7] was seen in one case.

Over half of approximately 350 patients with reported TTP are female.[2] Twenty-five cases of biopsy-proved TTP which occurred during pregnancy[4, 8–16] and two cases which developed post partum[15, 17] have been reported previously. These are summarized in Table I. Five patients[8–12] survived longer than 6 months post partum. At the time of report only one had survived longer than 2 years.[10] The fetus survived in seven antepartum cases and in the two postpartum

Table I. Previously reported cases of TTP associated with pregnancy

Ref. No.	*Year*	*Age*	*Race*	*Gravidity*	*Parity*	*Outcome*	*Treatment*	*Infant*
8*	1963	21	N.R.‡	1	1	Died 8 mo. pp.§	Steroids Blood Splenectomy 6 mo. pp.)	Viable, 37 wk.
9* (case 1)	1968	19	W	1	0	Survived	Steroids	Stillborn, macerated, 5 mo.
				2	1	Died 2 mo. pp. or 24 mo. after first pregnancy	Splenectomy 9 mo. following first pregnancy	Stillborn, 7 mo.
10*	1968	22	W	1	0	Alive 10 yr.	Steroids Splenectomy 3 mo. gestation	Term, viable
11*	1971	29	N.R.	1	0	Died 7 mo. pp.	Steroids Heparin	Viable, 6 mo. died 19 hr.
12*	1975	25	N.R.	3	2	Alive 10 mo. pp.	Steroids Aspirin Dipyridamole Blood Splenectomy 16 days pp.	Normal infant, 3,090 grams
13	1950	25	W	N.R.	N.R.	Died 14 days	None	Abortion, 10 wk.
20	1955	19	W	1	0	Died 11 days pp.	Steroids Digoxin Penicillin	Viable, 1,700 grams
21 (case 9)	1958	32	W	2	1	Died 4 days pp.	Blood	Stillborn, 6 mo.
21 (case 11)	1958	31	B	1	0	Died 8 days pp.	Steroids Blood	Stillborn, 9 mo.
22 (case 1)	1959	32	W	3	2	Died 3 days pp.	Steroids Antibiotics Blood	Macerated, 1,100 grams
22 (case 11)	1959	31	B	1	0	Died 5 days pp.	Steroids Antibiotics Blood	Stillborn, 2,590 grams
23 (case 2)	1960	22	W	N.R.	N.R.	Died 8 days pp.	Antihypertensive Blood	Stillborn, 6 mo.
24	1962	36	B	9	8	Died 6 hr. pp.	Steroids Blood Oxygen	Stillborn, 1,900 grams
25	1962	32	W	2	1	Died ante partum	Blood Folic acid Vit. B_{12}	Normal infant unable to resuscitate after cesarean section
26	1963	28	N.R.	6	4	Died 4 days pp.	Steroids Blood Magnesium sulfate	Viable, 1,984 grams
27 (case 13)	1966	33	B	N.R.	N.R.	Died 3 wk. pp.	Steroids Antibiotics Blood	Abortion, 5 mo.
27 (case 14)	1966	35	W	N.R.	N.R.	Died 2 days pp.	Steroids Antibiotics Blood	Stillborn, 6 mo.
14	1966	17	N.R.	1	0	Died 2 days pp.	Steroids Blood Platelets	Viable, 8 mo.
9 (case 2)	1968	36	W	N.R.	N.R.	Died 7 days pp.	Steroids	Stillborn, 6 mo.
4	1970	21	W	1	0	Died 29 days pp.	Steroids Antibiotics	Stillborn, 8 mo.
15 (case 1)	1972	15	B	1	0	Died 2 days pp.	None	Stillborn, 8 mo.
15 (case 2)	1972	18	B	1	0	Died 5 days pp.	None	Stillborn, 6 mo.

*Long-term survival.
†Post partum.
‡N.R. = Not reported.
§pp. = Post partum.

Table I.—Cont'd

Ref. No.	*Year*	*Age*	*Race*	*Gravidity*	*Parity*	*Outcome*	*Treatment*	*Infant*
15 (case 3)	1972	18	W	1	0	Died 5 days pp.	Steroids Blood Platelets Heparin	Viable, term
16 (case 3)	1973	21	N.R.	N.R.	N.R.	Died on hospital day 13	Steroids Dextran	2 mo., not aborted
16 (case 8)	1973	25	N.R.	N.R.	N.R.	Died on hospital day 5	Steroids Heparin Splenectomy	8 mo., not delivered
17†	1958	21	W	2	1	Illness 6 days pp. died 8 days pp.	Blood	Viable
15 (case 4)†	1972	39	B	13	11	Illness 7 days pp. Died 23 days pp.	Steroids Blood Heparin Dextran Albumin Peritoneal dialysis	Viable, term

cases. Corticosteroids were administered to most patients. Splenectomy was performed on five patients, including four of the five who survived more than 6 months after delivery. Since a long-term survivor of TTP associated with pregnancy was carried to term after the discovery of TTP at 3 months of gestation, it would appear that pregnancy does not influence the course of TTP. Conversely, it appears that TTP has the same effect upon the pregnant as upon the nonpregnant patient. In both groups there is approximately a 10 per cent incidence of prolonged survival.

The patient in this report, in whom no underlying disease was identified, was treated unsuccessfully with corticosteroids, platelet aggregation inhibitors, splenectomy, and exchange transfusion. She exemplifies the generally poor prognosis of patients with TTP in spite of intensive treatment. The other patient, a long-term survivor, was treated with corticosteroids and heparin. This patient appears to confirm the belief that corticosteroids are especially beneficial when TTP occurs in conjunction with glomerulonephritis.[6] Although heparin was used, it has never been demonstrated to be clearly beneficial in the treatment of TTP and, as in this patient, its value remains controversial.

Schwartz, Rosenberg, and Coopenberg[18] reviewed all long-term survivors of TTP in 1972. All 34 patients were treated with corticosteroids. Three patients were treated with these agents alone, 25 had a splenectomy also performed, and six received additional agents, including dextran. They concluded that corticosteroids are essential in the treatment and when combined with the splenectomy offer the best chance of cure. Since 1972 several reports have encouraged the additional use of agents to inhibit platelet aggregation. Faguet and King[2] reported successful treatment with corticosteroids, dextran, and aspirin. Rossi, Redondo, and Borges[19] reviewed six patients who were successfully treated with corticosteroids and various inhibitors of platelet aggregation, including aspirin, dextran, and dipyridamole. These encouraging results indicate that the combination of corticosteroids and inhibitors of platelet aggregation is a reasonable primary form of management of all patients with TTP. If a rapid response to these agents does not occur, splenectomy would seem indicated.

REFERENCES

1. Moschcowitz, E.: An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries—An undescribed disease, Arch. Intern. Med. **36:** 89, 1925.
2. Faguet, G. B., and King, M. B.: Thrombotic thrombocytopenia purpura: Treatment with antiplatelet agents, Am. J. Med. Sci. **268:** 113, 1974.
3. Cuttner, J.: Splenectomy, steroids and Dextran-70 in thrombotic thrombocytopenia purpura, J. A. M. A. **227:** 397, 1974.
4. Clincopathological conference: Fever, abdominal pain, and eclampsia, Va. Med. Mon. **97:** 174, 1970.
5. Pritchard, J. A., Weisman, R., Ratnoff, O. D., and Vosburgh, G. J.: Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy, N. Engl. J. Med. **250:** 89, 1954.
6. Umlas, J., and Kaiser, J.: Thrombohemolytic thrombocytopenic purpura (TTP)—A disease or a syndrome?, Am. J. Med. **49:** 723, 1970.
7. Neame, P. B., Lechago, J., Ling, E. T., and Koval, A.:

Thrombotic thrombocytopenic purpura: Report of a case with disseminated intravascular platelet aggregation, Blood **42:** 805, 1973.
8. Case Records of the Massachusetts General Hospital: Case 74, N. Engl. J. Med. **269:** 1195, 1963.
9. Piver, M. S., Lisker, S. A., Rowan, N., et al.: Thrombotic thrombocytopenic purpura during pregnancy, AM. J. OBSTET. GYNECOL. **100:** 302, 1968.
10. Hill, J. B., and Cooper, W. M.: Thrombotic thrombocytopenic purpura: Treatment with corticosteroids and splenectomy, Arch. Intern. Med. **122:** 353, 1968.
11. Perel, I. D., and Forgan-Smith, W. R.: Thrombotic thrombocytopenic purpura presenting as eclampsia, Aust. N. Z. J. Obstet. Gynaecol. **12:** 257, 1972.
12. Barrett, C., and Marshall, J. R.: Thrombotic thrombocytopenic purpura, Obstet. Gynecol. **46:** 231, 1975.
13. Gore, I.: Disseminated anteriolar and capillary platelet thrombosis: A morphologic study of its histogenesis, Am. J. Pathol. **26:** 155, 1950.
14. Case Records of the Massachusetts General Hospital: Case 50, N. Engl. J. Med. **275:** 1125, 1966.
15. Moon, E. C., and Kitay, D. Z.: Hematological problems in pregnancy. II. Thrombotic (thrombohemolytic) thrombocytopenia purpura, J. Reprod. Med. **9:** 212, 1972.
16. Jaffe, E. A., Nachman, R. L., and Merskey, C.: Thrombotic thrombocytopenic purpura—Coagulation parameters in twelve patients, Blood **42:** 499, 1973.
17. Harrison, H. N.: Thrombotic thrombocytopenic purpura occuring in the puerperium, Arch. Intern. Med. **102:** 124, 1958.
18. Schwartz, J., Rosenberg, A., and Coopenberg, A. A.: Thrombotic thrombocytopenic purpura: Successful treatment of two cases, Can. Med. Assoc. J. **106:** 1200, 1972.
19. Rossi, E. C., Redondo, D., and Borges, W. H.: Thrombotic thrombocytopenic purpura: Survival following treatment with aspirin, dipyridamole, and prednisone, J. A. M. A. **228:** 1141, 1974.
20. Miner, P. F., Nutt, R. L., and Thomas, M. E.: Thrombotic thrombocytopenic purpura occurring in pregnancy, AM. J. OBSTET. GYNECOL. **70:** 611, 1955.
21. O'Brien, J. L., and Sibley, W. A.: Neurologic manifestations of thrombotic thrombocytopenic purpura, Neurology **38:** 55, 1958.
22. Reisfield, D. R.: Thrombotic thrombocytopenic purpura and pregnancy, Obstet. Gynecol. Survey **14:** 303, 1959.
23. Chung, E. B., and Gomez-Acebo, J.: Thrombotic thrombocytopenic purpura: A report of two cases with some unusual features, Georgetown Med. Bull. **14:** 137, 1960.
24. O'Leary, J. A., and Marchetti, A. A.: Thrombotic thrombocytopenic purpura in pregnancy, AM. J. OBSTET. GYNECOL. **83:** 214, 1962.
25. Reisfield, D. R.: Death from thrombotic thrombocytopenic purpura during pregnancy, Obstet. Gynecol. **19:** 517, 1962.
26. Solomon, W., Turner, D. S., Block, C., and Posner, A. C.: Thrombotic thrombocytopenic purpura in pregnancy, J. A. M. A. **184:** 587, 1963.
27. Amorosi, E. L., and Ultmann, J. E.: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature, Medicine **45:** 139, 1966.

Sexual experimentation and pregnancy in young black adolescents

MARIA GISPERT, M.D.
RUTH FALK, PH.D.
Chapel Hill, North Carolina

Young black adolescents (13 to 16 years of age) and their parents were interviewed and psychological tests were administered. They were divided into three groups; (1) abortion group, (2) pregnancy to term group, and (3) a control group of never-pregnant adolescents matched by age and socioeconomic status. We focus the present report on their performance in school and educational goals, sexual experimentation to intercourse, their use of contraceptives, theirs and their parents' attitudes toward abortion, their reaction to their pregnancy in the two pregnant groups, and their attitudes in choosing for or against abortion.

ADOLESCENCE is generally viewed as a period of turmoil. Psychoanalytic writings tend to describe numerous psychiatric symptoms that appear, change, and disappear during adolescence as part of the normal growing-up process.[1]

The psychoanalytic viewpoint emphasizes the channeling of sexual impulses and postponement of sexual experimentation as a necessary step in the adolescent process and the occurrence of sexual experimentation leading to intercourse before marriage has been generally considered sexual "acting out" (especially in the female).[2]

From anthropological studies, we know that there are wide variations in how sexual activity is considered by different cultures. With the present changes in attitudes and behavior in the sexual sphere of our societal norms and with the advance in contraceptive methods it is becoming very difficult to define what kind of sexual expression (holding hands, kissing, all stages of petting or sexual intercourse) is considered normal and healthy for a particular age. Since acceptable sexual behavior is so culturally bound, the use of overt sexual expression as a criterion for intrapsychic pathology is becoming increasingly questionable.

Schmideberg[3] defined the factors which delay heterosexual relations in adolescence in *this* culture as (1) strong family attachments, (2) idealizations of love and marriage, (3) religious and other cultural ideas, (4) adult supervision and avoidance of excessive erotic stimulation, and (5) various forms of sublimations such as physical activities and cultural interests. In the study to be reported, we address ourselves to several of these factors. When sexual intercourse starts at an early age, the chance of pregnancy in adolescence increases.

On a national level, Kantner and Zelnick[4] found that among sexually active 15- to 19-year-old girls, nearly three out of 10 became pregnant. Locally, in the state of North Carolina, Steahr[5] reported that in contrast to a general trend toward decrease, nonwhite birth rates for girls 15 through 19 years of age have remained at the same level as previously.

Background, history, and general explanation of the present study

An unwanted pregnancy in early adolescence is a very unfortunate event in a variety of ways for the girl who experiences it, for the family which most of the time has to take the financial and emotional burden of rearing or helping to rear the child, sometimes for the male involved, and most of all for the unwanted child.

We started seeing patients who were requesting an abortion at N.C.M.H. in the latter part of 1969. The state of North Carolina had passed an amendment to

From the Child Psychiatry Division, Department of Psychiatry, U.N.C. School of Medicine, University of North Carolina at Chapel Hill.

Research funded by the Maternal and Child Health Division of the National Institutes of Health, Grant No. R01 HD 05952.

Received for publication May 16, 1975.

Revised November 24, 1975, and February 16, 1976.

Accepted March 1, 1976.

Reprint requests: Maria Gispert, M.D., Child Psychiatry Division, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514.

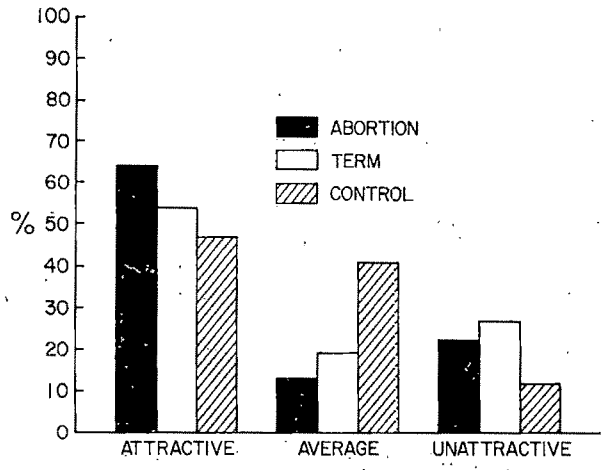


Fig. 1. Appearance. Chi square = 17.550 with 4 degrees of freedom; significance = 0.0015. Number of missing observations = 20.

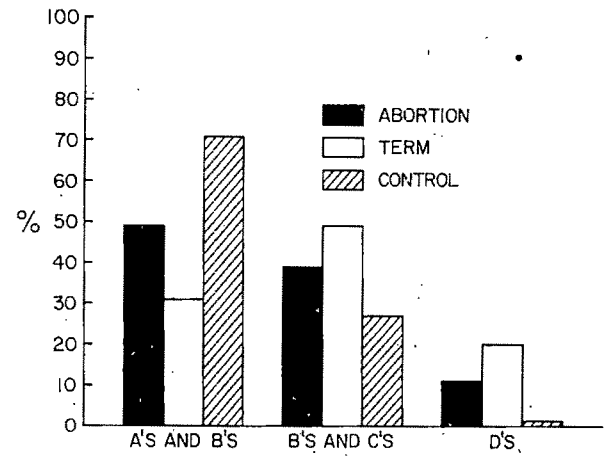


Fig. 3. School performance. Chi square = 25.744 with 4 degrees of freedom; significance = 0.001. Number of missing observations = 1.

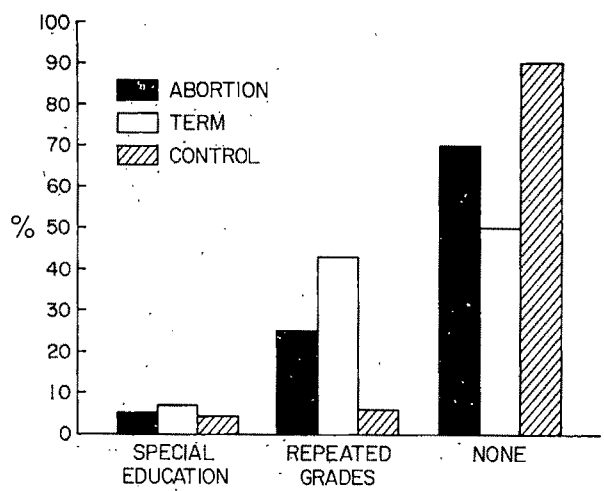


Fig. 2. Educational problems. Chi square = 25.750 with 4 degrees of freedom; significance = 0.001. Number of missing observations = 22.

the existing abortion law in May, 1967, that permitted interruption of a pregnancy by a doctor "If he could reasonably establish, among other things, that there was substantial risk that continuance of the pregnancy would threaten the life or gravely impair the health of the said woman." The terms "substantial risk" and "gravely impair" the health of the woman were vague and were interpreted in different ways by different doctors. Since physical health was seldom threatened, the mental health of the woman was to be considered more often. In the beginning, three physicians needed to agree and sign the recommendation for the abortion and it was generally assumed that one of the three would be a psychiatrist. Being a child psychiatrist very interested in adolescents, Dr. Gispert was asked to see the pregnant teenagers (16 and younger) who were requesting a "therapeutic abortion." Since the adolescent is considered a minor, one of the parents has to consent and sign the approval form, so at least one of the parents was also interviewed—separately—after the interview with the girl. In several cases, when discrepancies in their stories, disagreements about their wishes, or problems in the relationship and/or communication in the family appeared, and it seemed that these would interfere with the resolution of the crisis, the adolescent and the parent were seen together and the problems were further discussed.

Since abortion was such a controversial issue and the psychiatric literature had very conflicting reports about the effects of abortion on women, we decided to do a follow-up of the first 71 patients seen, about 8 months after the abortion.[6]

Present study

We are currently carrying out a longitudinal study on three groups of adolescent girls 13 to 16 years of age. There have been girls 10 and 11 years of age in the abortion group but they were unable to complete the psychological testing. In this paper, we are confining ourselves to the black teenagers, since we could not locate a large enough group of white adolescents who carried their pregnancy to term for making statistically meaningful comparisons.

We have designated the groups as follows: in the abortion group are girls who became pregnant and chose abortion; the term group comprises girls who

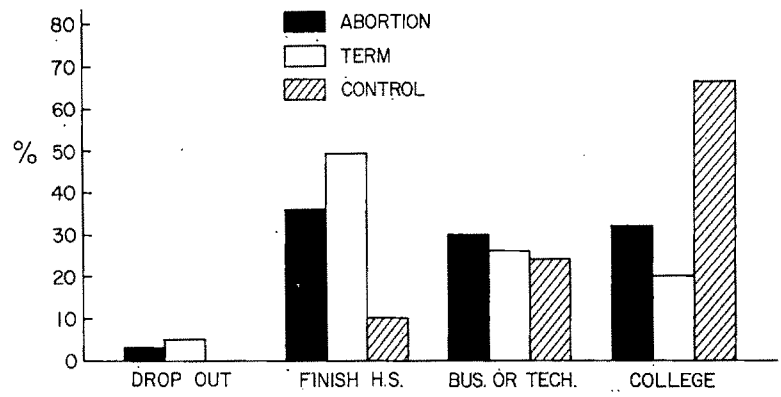


Fig. 4. Educational goals. Chi square = 39.941 with 6 degrees of freedom; significance = 0.001. Number of missing observations = 5.

chose to have their baby; the control group is composed of girls from a similar age and socioeconomic background who have not had a pregnancy. We will present some observations and comparisons obtained at the time of the initial interview with the girls and their parents.

Method

We gather information through semistructured interviews with the girls and simultaneous but separate interviews with one or both parents, using a multichoice questionnaire completed by the interviewer, with ample space to record verbatim both girl's and parents' statements. We administer a psychological test, the Rodgers Combined MMPI-CPI (Minnesota Multiphasic Personality Inventory and the California Psychological Inventory).

In order to obtain norms for the MMPI and CPI for this age population, we administered the test to a sample of 465 adolescent girls from eighth, ninth, tenth, and eleventh grades in the Chapel Hill and Durham city school systems. The control sample, matched by age and race, was selected from this group.

The interview focuses on these general area: the subject's functioning in the family, in school, with peers; her sexual history (dating); the impact of the pregnancy (in the two pregnant groups); plans for the future in reference to the care of the baby (in the term group); life goals such as marriage, number of children, educational plans, and occupational plans.

Results

The following data were compiled from interviews with 214 black adolescents. The mean ages of the 80 abortion candidates, the 64 pregnancy-to-term subjects, and the 70 control subjects were 14.6, 16.4, and 15.0 years, respectively.

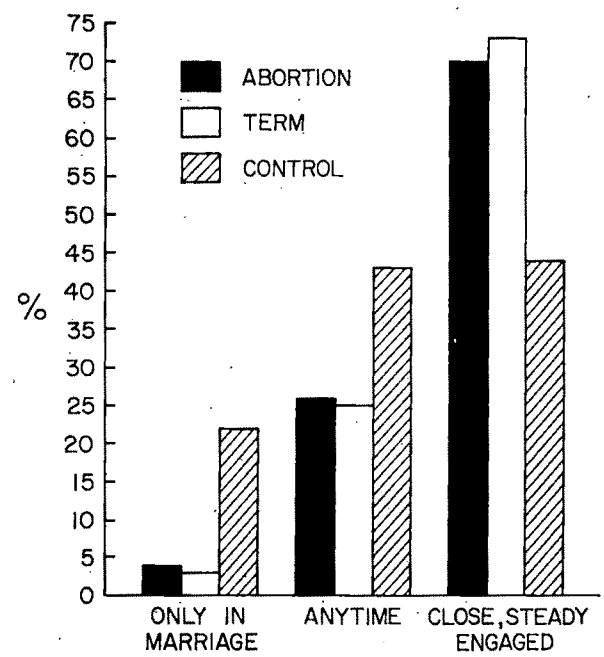


Fig. 5. Attitudes about when intercourse is acceptable. Chi square = 21.63 with 4 degrees of freedom; significance = 0.001. Number of missing observations = 16.

Appearance. The interviewer made a subjective evaluation of the attractiveness of the girl which included her physical appearance, her demeanor, and her reaction to us (Fig. 1).

Education. The girls' academic performance in school was categorized according to whether they had had no problems, had attended a Special Education class, or had repeated one or more grades (as judged by a discrepancy between chronological age and grade level) (Fig. 2).

School performance. The grades obtained correlated with the above information in that across all

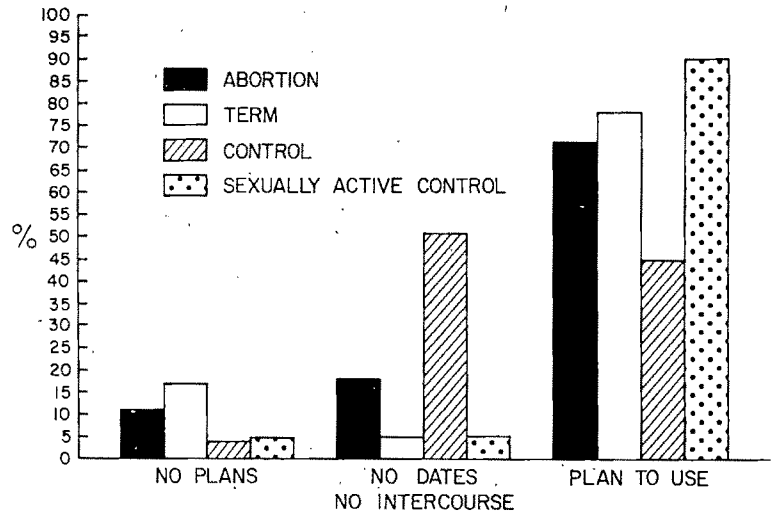


Fig. 6. Contraceptive plans. Chi square = 42.00 with 6 degrees of freedom; significance = 0.001. Number of missing observations = 13.

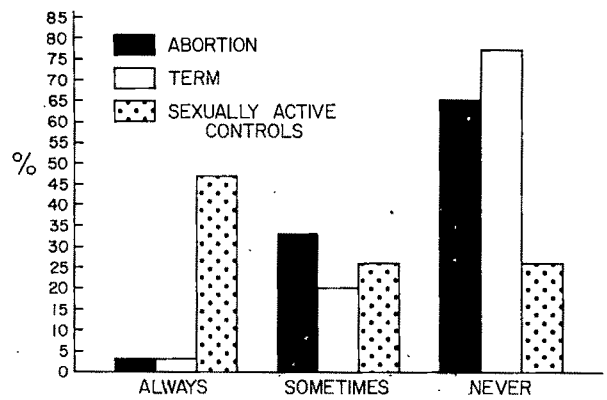


Fig. 7. Use of contraceptives prior to pregnancy. Chi square = 48.49 with 4 degrees of freedom: significance = 0.001. Number of missing observations = 3.

grade levels the control subjects did best, with the abortion group following and then the term group. The term girls in this sample were actually in a special school for pregnant girls and our numbers do not include the numerous girls who dropped out of school due to a pregnancy (Fig. 3).

Educational goals. Educational end-goals follow a pattern similar to that of educational achievement (Fig. 4).

Dating. The girls were allowed by their parents to "take company" at a mean age of 14 for the abortion group, 13 for the term group, and 14 for the control group, go "group dating" a few months later, and "go on dates alone" in the same year.

Relation with putative father. Half of the abortion group had a relationship that had lasted less than 6 months, and half more than 6 months. In the term group 78 per cent reported a relationship lasting more than 6 months. Of those who described the relationship as casual, 46 per cent were abortion subjects and 25 per cent term girls. Those who described it as "serious" included 48 per cent of the abortion group and 75 per cent of the term group.

Table I. Time between first intercourse and pregnancy*

Pregnancy occurring	*Abortion group (%)*	*Term group (%)*
Within 1 yr. of first intercourse	38	17
From 1 to 2 yr.	38	41
More than 2 yr.	23	41

*Chi square = 13.1946 with 2 degrees of freedom; Significance = 0.005.

Another perspective of the relationship with the boyfriend is obtained through the question about who they told first of their suspicion of being pregnant. The abortion group told the boyfriend first in 30 per cent of the cases and the term group in 50 per cent. The mother was told first in 36 per cent of the abortion group and 20 per cent of the term group. Only one abortion patient told her father first.

The putative father was not told of the pregnancy at all in 44 per cent of the abortion group as compared with only 5 per cent of the term group. Different reasons were given for not involving the putative father. Sometimes the girl had "broken up" with the boy and preferred to keep him completely out of the problem. The fear was expressed that he might tell

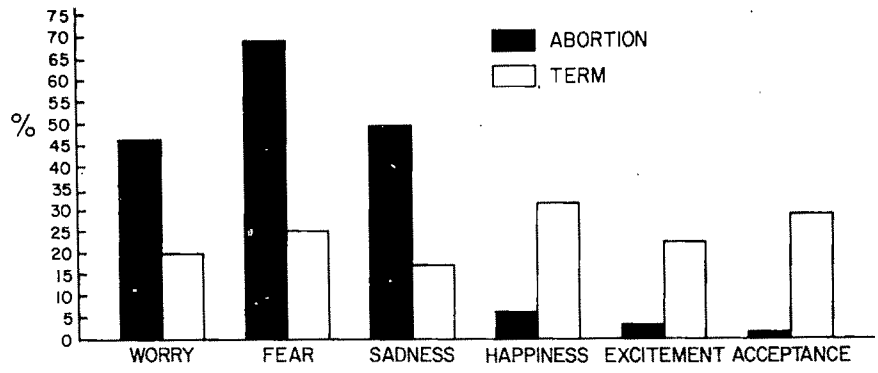


Fig. 8. Girl's reaction to pregnancy. Worry: Chi square 9.44; significance = 0.002. Fear: Chi square 25.50; significance = 0.001. Sadness: Chi square 14.26; significance = 0.001. Happiness: Chi square 13.79; significance = 0.001. Excitement: Chi square 11.62; significance = 0.001. Acceptance: Chi square 24.98; significance = 0.001.

others. Some of the girls were planning to continue dating the same boyfriend without telling him of the pregnancy or else they thought of perhaps informing him after the abortion.

Attitudes toward sexual intercourse. These percentages (Fig. 5) are very similar to the findings reported by Sorensen.[7]

Age at first intercourse. There does not seem to be any major difference between the two pregnant groups with regard to the age at which they started to have intercourse. About one third of each group began at 13 years or younger, a third at 14, and a third at 15, with less than 10 per cent beginning intercourse at 16. Of the control girls, 72 per cent denied having had intercourse, and only a fourth were considered sexually active. Of the sexually active controls, almost half started having intercourse at 15 years of age.

Intercourse experience. In the two groups which had become pregnant, the pregnancy occurred when the girls reported having had intercourse with the putative father "less than five times" in 39 per cent of the abortion group but in only 18 per cent of the term group. The term girls more frequently reported having intercourse more than 15 times (51 per cent), as compared with the abortion group (26 per cent), with the six to 15 times incidence being almost equal for both groups (abortion, 26 per cent; term, 32 per cent). These differences are significant at the 0.005 level.

The periods of time elapsing in the two groups between first intercourse and the occurrence of pregnancy are presented in Table I.

Contraceptive plans. The control subjects were divided between the ones who denied having had intercourse and those who said they had (Fig. 6). We assumed the two groups to be different, in that the latter had been confronted with the need to use contraceptives or risk a pregnancy.

Use of contraceptives. The group who "always" used a contraceptive was obviously not well represented in the two pregnant groups (Fig. 7). In these cases the pregnancy can be explained only by contraceptive failure (IUD's, "busted" condoms, etc.). The girls who claimed to be taking the pill were not included in the "always" category because it was found that they were taking their pills irregularly or had discontinued their use. This reminds us that the effectiveness of the birth control pill is contingent on regular ingestion and there is great possibility of consumer error, especially in this age group.

The use of contraceptives in the abortion and term groups was cross-tabulated with the frequency of intercourse, revealing an increased use of contraceptives as intercourse increased from "less than five times" to "more than 15 times." The number of girls "never" using contraceptives decreased, but not drastically, with the regularity of intercourse (from 83 to 61 per cent).

Girl's reaction to the pregnancy. Unfortunately, the two groups of pregnant adolescents were first interviewed at different stages of their pregnancy (Fig. 8). The abortion group were on the average in their fourteenth week and the term girls in their twenty-eighth week. This fact alone probably influenced the responses to a significant degree.

When the pregnancy appeared to them as a strong possibility, two thirds of the abortion group and one third of the terms had numerous fears. The most frequent fears were about their parents' reactions, anticipating anger and criticism, and in some cases voicing fears of bodily harm, or of being thrown out of their homes. Others were afraid of what the shock might do to the parents (if they were sick, nervous, alcoholic, etc.). Most frequently, it was not only the pregnancy per se that they were concerned about but also the fact that the parents would know about their

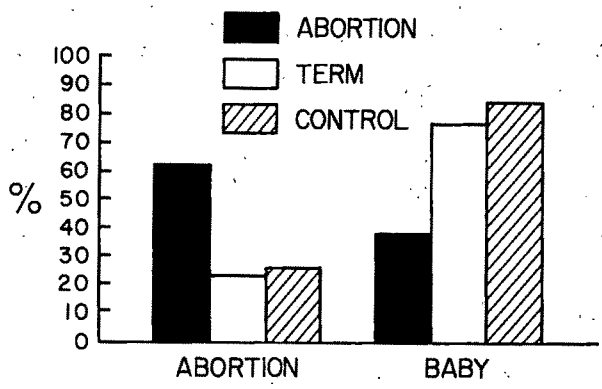


Fig. 9. Outcome of friends' or relatives' pregnancy. Chi square = 28.07 with 2 degrees of freedom; significance = 0.001. Number of missing observations = 75.

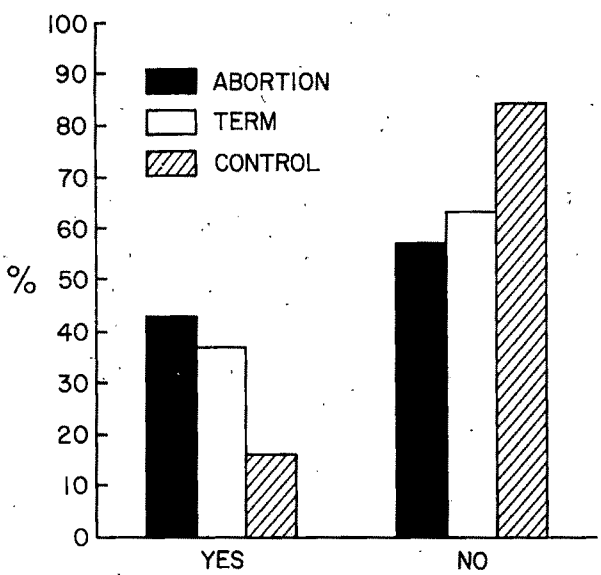


Fig. 10. Sisters of subjects who had become pregnant before 20 years of age. Chi square = 13.60 with 2 degrees of freedom; significance = 0.001. Number of missing observations = 14.

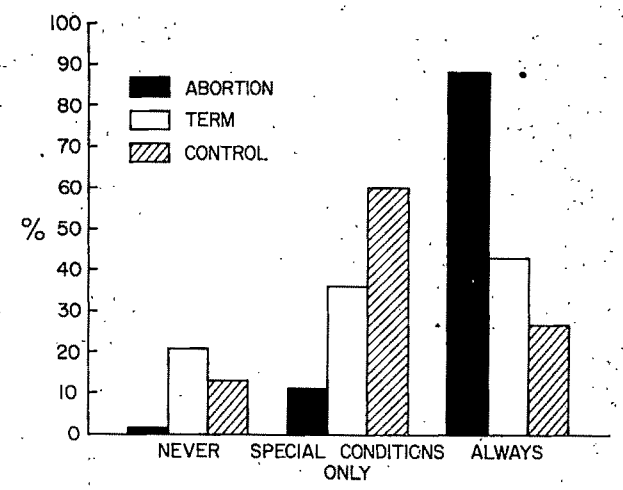


Fig. 11. Girl's attitude toward abortion. Chi square = 59.032 with 4 degrees of freedom; significance = 0.001. Number of missing observations = 24.

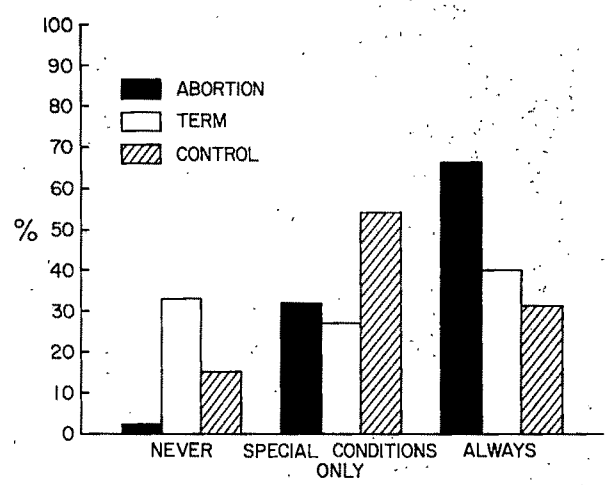


Fig. 12. Parents' attitudes toward abortion. Chi square = 25.704 with 4 degrees of freedom; significance = 0.001. Number of missing observations = 73.

sexual activity. The majority reported that their expectations had been much worse than what actually happened when the parents were informed.

Outcome of friends' or relatives' pregnancies. As one would expect, term girls reported a greater number of friends who had had babies (Fig. 9). Abortion candidates mentioned a greater proportion of friends who had had abortions. We feel that both groups would probably have under-reported abortions, however, since most people do not discuss abortions after the event. The control girls mentioned that they knew of three times more cases of friends or relatives who had had babies than abortions.

Sisters of girls who had become pregnant before 20 years of age. More abortion than term patients reported that their sisters had become pregnant before they were 20 years old (Fig. 10). Moreover, it is interesting that the two pregnant groups' sisters were markedly more prolific than those of the control group.

Girls' and parents' attitudes toward abortion. We noted that the girls' attitudes toward abortion were slightly more liberal than their parents'. However, the same pattern was present (Figs. 11 and 12).

Reasons for seeking termination of the pregnancy. The pregnant adolescents who seek interruption of their pregnancy report the following reasons: 86 per cent do not want a child now (a simple choice); 79 per cent want to continue their education, and they view a child as an interruption to or impairment of this goal;

79 per cent see themselves as emotionally immature, not ready to take the responsibility and provide the care that a child requires; 67 per cent feel their body is not fully developed; 42 per cent say that their parents are unwilling or unable to help them with the child; 28 per cent are afraid of community criticism (scandal); 27 per cent feel that giving the child up for adoption would be unacceptable to them; 19 per cent mentioned that abortion would help to avoid family strife; 17 per cent mentioned that financial problems at home were an important factor; 13 per cent said that breaking up with the boyfriend (putative father) was a major consideration.

Other reasons very seldom mentioned were that the boyfriend refused to marry her, that they do not wish to get married for this reason, and medical causes.

Psychological testing—MMPI. We used a control group of 437 girls to construct our own norms. Twenty-eight tests were considered invalid and were excluded, as were profiles from girls who were known to have had a pregnancy. A brief preliminary scale-by-scale comparison of the MMPI data was completed for all three groups. All results reported are significant at better than the 0.05 level.

For all ages, both the term girls and the abortion group suffered more severely from feelings of despair and worthlessness than did the controls. They were less buoyant physically and showed a decreased energy level. In addition, the abortion group alone scored higher than the control group on a scale reflecting degree of family disturbance. This is to be expected, in that an illegitimate pregnancy was more at variance with the family's goals and values in this group than was true of the term group families. The term girls felt more chronically socially isolated than did the control subjects and the abortion girls and this was particularly so in the younger age group (14 and younger). Girls having their babies were thus dislocated from peer and family interactions, and had been so for some time. The older term girls (15 and older) seemed to be feeling a sense of social disgrace and were trying to make themselves look good, whereas this was not the case with control subjects.

Since psychological testing was administered to the experimental groups during the crisis period represented by a pregnancy with different expected outcomes, no conclusions can be drawn about the chronicity or acuteness of these emotional reactions when comparisons are made across any groups. In other words, no *causal* inferences can be drawn about psychological factors which might identify a "high-risk" population.

We had a small sample of five control girls (not enough for a statistical comparison) who later became pregnant. Four of these girls scored above the limit on the F scale which we had selected as the cut-off point for a valid profile. It seems that these "out-of-controls" were either unable to understand the questions well enough to answer appropriately, or were generally dissatisfied with their lives and in a state of constant rebelliousness. This ratio of 4 to 5 "over the limit" F-scale scores diverged widely from the ratio found in all three groups as a whole.

We felt that the 1973 Supreme Court decision would have a significant impact on attitudes concerning abortion and the illegitimate pregnancy itself. Comparing MMPI profiles obtained from abortion candidates before and after 1973, we found the pre-1973 group tended to repress and deny bodily feelings of early pregnancy and were relatively pessimistic about their future lives. After 1973, the girls were able to be more realistic, in that they allowed themselves to be aware of the physiologic changes of pregnancy. They were also more optimistic about the future, although at the moment, naturally, feeling somewhat "blue." It seems, then, that the legalization of abortion has helped free illegitimately pregnant teenagers seeking a termination of their pregnancy from the attitudes and fears which could obscure their awareness and acknowledgment of the bodily changes occurring in them. Nowadays, too, these girls can look forward to their future lives with more genuine pleasure and hope.

Comment

The age of the girl at conception is an important factor in deciding the outcome of the pregnancy. Our society grants adolescents who have reached 16 years of age several privileges and the permission to assume certain responsibilities such as a driver's license, a worker's permit, etc., which provide independence from parents, mobility, and autonomy. Similarly, some girls who are already 16 at the onset of their pregnancy express opinion in favor of carrying the pregnancy such as; feeling old enough to care for a child, knowing that they can legally drop out of school, having friends and relatives of a similar age who have children, making it more difficult for them to break away from an accepted social pattern, having a boyfriend, usually older than the girl, who has offered either emotional and/or financial support if she continues with the pregnancy. At 16, the parents usually feel that the adolescent is more able to make her own decisions and to care for a child. Also, if the 16-year-old girl disagrees with her parents in reference to the outcome of the pregnancy, her parents and others would be more likely to respect her wishes due to her "maturity." The

younger the girl, the more justified she and parents feel in seeking an abortion. Parents exert more pressure on the younger adolescents (10 to 14 years of age) to terminate the pregnancy unless they themselves are willing and able to assume the parenting role for the offspring.

In general, the girls in the three groups were physically healthy, attractive, and related well to the interviewer.

The nonpregnant control girls reported the fewest problems in school and, judged by their grades, performed better and had higher educational goals for the future. We can speculate that their interest and success in school contributed to their more cautious heterosexual experimentation. The abortion group was intermediate between the control and the term groups. The pregnancy-to-term girls as a group had more difficulties in school, reporting lower grades and striving for less formal education. We can assume that the pregnancy curtailed their educational goals but it is still apparent that they were poorer students before the pregnancy occurred. Having a baby may have been a mechanism to enhance their self-esteem, probably related to a romanticized idea of motherhood. Forcing a marriage did not seem to be the purpose of the pregnancy.

It is very difficult to ascertain the maturity and intimacy of the adolescents' heterosexual relationships. The reported dating stages varied from case to case. It is not surprising to find a high proportion of discontinuation of the relationship with the putative father, for in some cases no relationship had existed. Adolescence is an age for experimentation and learning. The younger the girl chronologically and emotionally, the less probable it is that she would sustain an on-going heterosexual relationship with a man who is only a few years older than she.

The fact that adolescents are willing to have sexual intercourse at earlier ages, while going steady or in a close relationship, exposes them to a pregnancy when they do not take appropriate preventive measures. We found that contraceptives were not used by the majority of adolescents. If they were tried at all, their use was not consistent. The control subjects who reported being sexually active used contraceptives more consistently.

The majority of the adolescents denied the wish to become pregnant and when they became aware of the pregnancy they had different reactions. The abortion group expressed more open discomfort and opposition to the continuation of the pregnancy, whereas the term group was more inclined to accept it, mainly because they and their parents were opposed to abortion in principle.

In all three groups the girls reported marked inability to talk with their parents about sexual activity and, in the case of the pregnant adolescents, the denial and reluctance to tell their parents about the pregnancy was mostly due to the obvious disclosure of the fact that they had experienced sexual intercourse. The attitude of secrecy and shame in reference to sexual intercourse interferes with the rational prevention of possible consequences such as a pregnancy, even though it does not seem to prevent the occurrence of sexual behavior as such.

Through personal interviewing of the girls and their parents and the psychological tests results, we have found that the adolescents in all three groups, as would be expected, have individual variations, and are in different stages of physical and emotional growth and development. All three groups have similarities and differences but no group showed a significant degree of psychopathology.

We thank Dr. Charles H. Hendricks, Chairman of the Obstetrics and Gynecology Department at the University of North Carolina School of Medicine, and his staff for help and collaboration and the personnel of the Durham and Hill, North Carolina, City School Systems.

REFERENCES

1. Freud, A.: Adolescence, Psychoanal. Study Child **13:** 255, 1958.
2. Deutsch, H.: Selected problems of adolescence: Illegitimate motherhood, Psychoanal. Study Child Monograph **3:** 106, 1967.
3. Schmideberg, M.: Psychiatric-social factors in young unmarried mothers, Soc. Casework **32:** 3, 1951.
4. Kantner, G., and Zelnik, M.: Contraception and pregnancy: Experience of young unmarried women in the U. S., Fam. Plann. Perspect. **5:** 1973.
5. Staehr, T.: North Carolina's Changing Population: Carolina Population Center, Chapel Hill, 1973, University of North Carolina.
6. Perez-Reyes, M. G., and Falk, R.: Follow-up after therapeutic abortion in early adolescence, Arch. Gen. Psychiatry **28:** 120, 1973.
7. Sorensen, R.: Adolescent Sexuality in Contemporary America, New York, 1973, World Publishing Company (Times Mirror).

Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn

DAVID MANCHESTER, M.D.
HAROLD S. MARGOLIS, M.D.
ROGER E. SHELDON, M.D.
Denver, Colorado

Indomethacin purportedly arrests premature labor by inhibiting the production of prostaglandins. Animal experimentation has demonstrated that prostaglandins are involved in the neonatal rerouting of the circulation. Experience with two neonates with disordered circulatory adjustments at birth following prenatal exposure to indomethacin indicates that indomethacin may interfere with these adjustments in man and favor the development of the serious oxygen dependency known as primary pulmonary hypertension of the newborn.

RECENT experiments in both animals[1, 6, 8] and human beings[13] demonstrating inhibition of labor by indomethacin* have led to its limited clinical use. Aspirin, which like indomethacin inhibits prostaglandin production, also appears to prolong gestation and labor.[7] However, the effects on the fetus of prostaglandins or their inhibition are still largely unknown. Of particular interest are the potential hemodynamic consequences of prostaglandin inhibition.

Case reports

Case 1. This baby girl was delivered by cesarean section to an 18-year-old gravida 3, para 0 woman whose pregnancy progressed normally until she presented in labor with painless vaginal bleeding at 33 weeks of gestation. An alcohol infusion failed to stop labor, and the mother was given 100 mg. of indomethacin rectally and 50 mg. by mouth. Labor subsided, and the mother was maintained on 25 mg. of indomethacin every 6 hours by mouth, for 4 days, receiving her last dose 4 hours prior to delivery. The membranes were not known to be ruptured, but the mother developed a fever and a foul vaginal discharge. She received one dose each of ampicillin and kanamycin about 4 hours prior to delivery. Oxytocin* stimulation of labor was attempted but, because of fetal tachycardia with late decelerations of the fetal heart rate, a cesarean section was performed under nitrous oxide anesthesia after thiopental induction. A 2,000 gram female infant was delivered through foul-smelling amniotic fluid. The Apgar scores were 1 and 3 at 1 and 5 minutes. Resuscitation included endotracheal intubation, positive-pressure ventilation, and intravenous albumin injection, which produced prompt improvement. The infant was given 40 per cent oxygen. Physical examination showed good color, mild retractions, no murmur, and an estimated gestational age of 35 weeks. Blood pressure, glucose, and body temperature were normal.

At 3 hours of age, the inspired oxygen concentration was decreased to 35 per cent. The patient immediately became cyanotic and lethargic. A chest film showed mild cardiomegaly but no evidence of infiltration consistent with pneumonia, hyaline membrane disease, or aspiration. The patient's blood, spinal fluid, and ear canal were cultured, and she was given ampicillin and kanamycin parenterally.

At 8 hours of age she was transported to a tertiary-care center, at which time she required 80 per cent

From the Division of Perinatal Medicine, Departments of Pediatrics and Obstetrics-Gynecology, University of Colorado Medical Center.

This work was supported by NIH Grants HD-00781, HD-00429, and 00065-12.

Received for publication December 30, 1975.

Accepted March 8, 1976.

Reprint requests: Roger E. Sheldon, M.D., Division of Perinatal Medicine, Container B-198, University of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colorado 80220.

**Indocin, Merck, Sharp and Dohme, West Point, Pennsylvania.*

*Pitocin, Parke, Davis & Co., Detroit, Michigan.

oxygen to maintain a Pa_{O_2} of 50 mm. Hg. Examination on admission confirmed the previous observations, and a chest roentgenogram showed possible cardiomegaly and normal or slightly decreased pulmonary vascularity. The patient required 100 per cent oxygen within an hour of admission. A 12 lead electrocardiogram was normal for age; hematocrit was 42 per cent; serum calcium was 3.5 mEq. per liter.

A provisional diagnosis of primary pulmonary hypertension of the newborn was made. Right radial and umbilical artery blood gases were identical. Within 2 hours of admission the patient began to improve and was stable in 50 per cent oxygen within another hour. There were no further complications, and the patient was transferred back to the referring hospital and was breathing room air the following day. The cultures proved negative.

Case 2. This 2,480 gram male infant was born at 34 weeks of gestation to a 38-year-old gravida 3, para 2 woman whose membranes had ruptured after a fall 7 weeks prior to delivery. At that time, the mother was hospitalized, and uterine contractions were treated for 7 days with bedrest and indomethacin, 50 mg. every 6 hours by mouth. The mother was also given intravenous antibiotics and was discharged after 1 week. She was instructed to take 50 mg. of indomethacin with 30 c.c. of Maalox every 6 hours, whenever she felt uterine contractions. She took one or two 50 mg. tablets each week for the next 6 weeks. Vaginal bleeding began 4 days prior to delivery, and she began taking 50 mg. every 6 hours, regularly. Her last dose came 12 hours before delivery.

Delivery was by breech extraction, after 4½ hour labor with oxytocin augmentation and mepivacaine* pudendal block. The mother had received 10 mg. of morphine 1½ hours prior to delivery and 200 mg. of secobarbital† 3½ hours prior to delivery. Apgar scores were 7 and 8, but the infant continued to be cyanotic, though he was in no respiratory distress. He was given 80 per cent oxygen and an umbilical artery catheter was inserted.

On admission to the referring nursery, the infant's temperature was 35.9° C., the blood pressure was 48/20 mm. Hg, and Dextrostix read 30 mg. per 100 ml. Initial physical examination found clear lungs, no heart murmurs, and an estimated gestational age of 34 weeks. A chest roentgenogram showed cardiomegaly but no infiltrates or other pathology. The patient was transferred to a tertiary center at 2 hours of age, breathing 90 per cent oxygen. During these 2 hours he received a small amount of intravenous fluid containing 2 mEq. of sodium bicarbonate, 25 units of heparin, and 2 mg. of hydrocortisone sodium succinate‡ per 100 ml. Upon arrival, the patient was tachypneic but with normal breath sounds; a systolic murmur and gallop rhythm were noted. An electrocardiogram was normal; the serum contained 3.8 mEq. per liter of calcium. Simultaneous right radial and umbilical Pa_{O_2} measurements differed by 34 mm. Hg. Fluid restriction and digoxin were begun, but within 5 hours of admission the patient's Pa_{O_2} was 105 mm. Hg while breathing 50 per cent oxygen. Right-to-left ductus shunting was no longer demonstrable and no murmur was heard. The patient was breathing room air at 48 hours of age.

Hyperbilirubinemia also became a problem, with total bilirubin remaining elevated (11 mg. per 100 ml.) on day 15. Direct Coombs test was negative; smears and reticulocyte counts were normal; bacterial and viral cultures were negative; the urine contained no reducing substances; thyroxin levels were normal. The patient was discharged at 16 days of age and has suffered no further complications.

*Carbocaine, Cook-Waite Laboratories, Inc., New York, New York.

†Seconal, Eli Lilly & Co., Indianapolis, Indiana.

‡Solu-Cortef, The Upjohn Company, Kalamazoo, Michigan.

Comment

Primary pulmonary hypertension of the newborn is a syndrome of neonatal arterial oxygen desaturation in the absence of parenchymal pulmonary disease or cardiac malformation. It is characterized by inappropriately high pulmonary vascular resistance and subsequent right-to-left shunting of blood at the foramen ovale and/or ductus arteriosus. Other synonymous terms include persistence of the fetal circulation, persistence of the fetal cardiopulmonary circulatory pathway, progressive neonatal pulmonary hypertension, and persistent pulmonary vascular obstruction of the newborn. It is not to be confused with so-called primary pulmonary hypertension of older children.

The condition has been documented in association with birth asphyxia, hypoglycemia, hypocalcemia, and hyperviscosity.[5, 10] Idiopathic cases have also been reported.[4] In the cases reported here, the syndrome occurred within 12 hours of maternal treatment with a drug known to increase pulmonary vascular reactivity in response to hypoxia in animals.[12] The interpretation of indomethacin's role in the first case is complicated by severe asphyxia, but the patient's apparent recovery from asphyxia followed by an exaggerated response to hypoxia at 3 hours of age suggests an altered vascular reactivity. In the second case, right-to-left shunting at the ductus arteriosus was documented in the absence of asphyxia, hypoglycemia, or hyperviscosity. The role of the borderline hypocalcemia is obscure, since no calcium supplements were given and no further calcium levels were determined.

Animal experiments have suggested that prostaglandins E and F are involved in regulation of vascular resistance in the ductus arteriosus and the pulmonary vascular bed. Prostaglandin E_2 has been used in human

infants to maintain a patent ductus arteriosus.[3] In utero blockade of prostaglandin production by indomethacin has produced constriction or closure of the ductus arteriosus in sheep and rats.[2, 9] Indomethacin-treated neonatal goats demonstrated a greater increase in pulmonary vascular resistance in response to hypoxia than control animals.[12] The latter study suggests that, in the presence of inhibited prostaglandin production, cardiopulmonary adaptation to extrauterine life may be abnormal, especially in the presence of hypoxia. In particular, the picture of primary pulmonary hypertension of the newborn due to elevated pulmonary vascular resistance appears to be a possible consequence.

The published data of Zuckerman and associates[13] on use of indomethacin in man does not include such relevant information as gestational ages, diagnoses, or postmortem findings on five infants who died within 48 hours of birth, after indomethacin failed to prevent delivery in 12 of 50 cases.[13] It is thus difficult to estimate whether or not this mortality experience is excessive.

Indomethacin has been given to a few additional obstetric patients in Denver without apparent perinatal problems. It is noteworthy that in none of the five asymptomatic cases known to us was the drug administered within 24 hours of delivery. Placental transfer and plasma clearance data on indomethacin in fetuses are lacking, but a serum half-life of 14.7 hours has been measured in newborns by Traeger and associates.[11] This might be consistent with the period of symptoms seen in our infants. In contrast, young women had serum half-lives measuring roughly 2½ hours.[11]

It is theoretically possible that inhibition of prostaglandin synthesis could produce aberrations of perinatal adaptation like those observed. As with any therapy, risks and benefits should be fully understood prior to widespread clinical use. Until more information is collected concerning the metabolic, hematologic, and hemodynamic effects of indomethacin on the fetus and newborn, use of this drug to prolong gestation should be limited to centers where high-quality observation and management of the fetus and newborn are promptly available. Delayed or improper management of problems like those reported here could be devastating.

REFERENCES

1. Chester, R., Dukes, M., Slater, S. R., and Walpole, A. L.: Delay of parturition in the rat by anti-inflammatory agents which inhibit the biosynthesis of prostaglandins, Nature **240:** 37, 1972.
2. Coceani, F., Olley, P. M., and Bodach, E.: Prostaglandins: A possible regulator of muscle tone in the ductus arteriosus (abst.), International meeting on prostaglandins, Florence, Italy, 1975, p. 151.
3. Elliott, R. B., Starling, M. B., and Neutze, J. M.: Medical manipulation of the ductus arteriosus, Lancet **1:** 140, 1975.
4. Gersony, W. M., Duc, G. V., and Sinclair, J. C.: "PFC" syndrome (persistence of the fetal circulation) (abst.) 42nd. Scientific Session, Circulation **39, 40**(Suppl. III): 87, 1969.
5. Gersony, W. M.: Persistence of the fetal circulation: A commentary, J. Pediatr. **82:** 1103, 1973.
6. Hertelendy, F.: Block of oxytocin-induced parturition and oviposition by prostaglandin inhibitors, Life Sci. **13:** 1531, 1973.
7. Lewis, R. B., and Schulman, J. D.: Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor, Lancet **2:** 1159, 1973.
8. Novy, M. J., Cook, M. J., and Manaugh, L.: Indomethacin block of normal onset of parturition in primates, Am. J. Obstet. Gynecol. **118:** 412, 1974.
9. Sharpe, G. L., Thalme, B., and Larsson, K. S.: Studies on closure of the ductus arteriosus. XI. Ductal closure in utero by a prostaglandin synthetase inhibitor, Prostaglandins **8:** 363, 1974.
10. Siassi, B., Goldberg, S. J., Emmanouilides, G. C., Higashino, S. M., and Lewis, E.: Persistent pulmonary vascular obstruction in newborn infants, J. Pediatr. **78:** 610, 1971.
11. Traeger, V. A., Nöschel, H., and Zaumseil, J.: Zur Pharmakokinetik von Indomethazin bei Schwangeren, Kreissenden und deren Neugeborener, Zentralbl. Gynäkol. **95:** 635, 1973.
12. Tyler, T. L., Wallis, R. G., Leffler, C. W., and Cassin, S.: Prostaglandins and the pulmonary vascular response to hypoxia in the neonate (abst.), Fed. Proc. **34:** 319, 1975.
13. Zuckerman, H., Reiss, U., and Rubinstein, I.: Inhibition of human premature labor by indomethacin, Obstet. Gynecol. **44:** 787, 1974.

Controlled trial of fetal intensive care

PETER RENOU
ALLAN CHANG
IAN ANDERSON
CARL WOOD
Melbourne, Victoria, Australia

A fetal intensive care unit was formed at the Queen Victoria Memorial Hospital in 1972. Because of some doubt concerning the value of fetal intensive care, a controlled clinical trial including all high-risk patients was performed. The trial clearly showed that intensive care is associated with improved neurologic and biochemical status of the neonate; however, it is possible that this improvement results from the use of fetal diagnostic tests or some other factor associated with intensive care. Sufficient evidence was gathered to warrant the continuation of fetal intensive care in this hospital, but in other countries, where funding is difficult to obtain, a controlled trial would appear justified.

BETWEEN 1967 and 1972 obstetricians used fetal intensive care on an elective basis, depending upon their attitude to the value of fetal heart rate (FHR) monitoring and fetal scalp blood collection. In 1972 a fetal intensive-care unit (FICU) was formed at the Queen Victoria Memorial Hospital which provided fetal surveillance for all high-risk pregnancies. The surveillance consisted of FHR monitoring and fetal scalp blood pH measurement. By this time most of the medical staff found the service attractive and monitoring was carried out in nearly all patients where the fetus was at increased risk. However, several of the senior obstetric staff members were skeptical of the value of the service, although still using it, and felt that improvement of fetal outcome may result only from the better obstetric surveillance associated with the presence of those doctors and nurses running the FICU.

Because of this and the fact that a number of people in other hospitals have expressed skepticism of the value of fetal intensive care, a controlled clinical trial was organized to estimate the advantage, if any, of fetal intensive care.

Received for publication September 9, 1975.

Accepted February 17, 1976.

Reprint requests: Dr. Peter Renou, Department of Obstetrics and Gynaecology, Monash University, The Queen Victoria Memorial Hospital, 172 Lonsdale St., Melbourne, 3000, Victoria, Australia.

Method

The FICU was organized by an experienced obstetrician who had previous experience of fetal monitoring. Special nursing and technical staff were attached to the unit in order to organize the application of the fetal monitor to the patient and the analysis of fetal scalp blood pH. The FHR was continuously monitored in patients who had a poor obstetric history, a medical or obstetric complication, an abnormal FHR detected by auscultation, or the presence of meconium in the amniotic fluid.

If the monitored FHR was abnormal, then fetal scalp blood pH was measured. Clinical management was determined by the combined assessment of the clinical history and the prognosis known to be associated with FHR and fetal scalp blood pH findings.[1] Information concerning an abnormal FHR or scalp blood measurement was given to the obstetrician in charge of the patient, as the intensive-care unit did not direct the clinical care of the patient.

The aim of the trial was to assess the effects, if any, of fetal monitoring on the course and conduct of labor and the fetal and maternal outcome.

All high-risk patients were selected for inclusion in the trial which commenced in March, 1974. Initially all eight obstetricians of the hospital referred such patients for inclusion in the trial. During the course of the trial one of the doctors withdrew his patients from the trial because he felt that intensive care was effective,

Table I. Indications for admission to trial in control and intensive-care group

	Control	*Trial*
Meconium in amniotic fluid	89	87
Abnormal FHR	10	11
Prolonged pregnancy	4	9
Hypertension	59	52
Proteinuria	24	11*
Elderly primigravida	4	4
Cardiac disease	4	2
Diabetes mellitus	5	5
Fetal growth retardation	4	8
Antepartum hemorrhage	1	5*
Prolonged labor	4	9
Low urinary estriol excretion	14	19
Total	222	218

*A significant difference exists between the incidence of this abnormality in the two groups, $p < 0.05$. However, the difference does not account for the differences in fetal outcome between the two groups shown in later tables.

Table II. Comparability of the control and intensive care groups

	Control	*Intensive care*	*Statistical test*
Maternal age (years)			
Mean	25.3	24.8	t = 0.60
S.D.	7.4	6.4	NS*
Parity			
0	89	91	$\chi^2 = 5.84$
1	44	37	NS
2	16	29	
3+	26	18	
Gestation (days)			
Mean	274	276	t = 1.66
S.D.	16	13	NS
Birth weight (Gm.)			
Mean	3287	3,260	t = 0.45
S.D.	551	550	NS

*NS = Not significant.

and that it would be unethical for a high-risk patient to be managed without such care. The patients were randomly allocated to a control or intensive care group. The results were analyzed after each group of 50 patients had been completed. This was to avoid unnecessary prolongation of the trial should the fetal intensive-care group prove superior to the control group.

The intensive care patients were managed in the manner already established by the FICU (see above). The control patients were managed by the nursing and medical staff without the aid of either the FHR monitor or scalp blood sampling.

A total of 350 patients equally divided between the control and intensive-care groups were admitted to the trial. The study was conducted over a duration of 13 months. During this time, 14 per cent of all obstetric patients were admitted to the trial as high-risk cases, the total number of deliveries being 2,500.

Table III. Labor

	Control	*Intensive care*	*Statistical test*
Length of labor (hr.)			
Mean	9.0	9.2	t = 0.28
S.D.	5.2	6.4	NS*
Induction-delivery interval (hr.)			
No.	75	73	
Mean	10.2	10.3	t = 0.12
S.D.	7.6	6.9	NS
Oxytocin use			
Maximum dose (mU./min.)			
No.	110	109	
Mean	20	19	t = 0.65
S.D.	19	18	NS
Duration (hr.)			
Mean	7.3	7.3	t = 0.06
S.D.	5.5	5.3	NS
IV fluid volume use (l)			
No.	175	175	
Mean	1.9	1.7	t = 0.63
S.D.	4.0	1.6	NS
Duration (hr.)			
Mean	7.6	7.6	t = 0.08
S.D.	8.0	6.9	NS
Ketonuria incidence			
0	143	138	$\chi^2 = 0.65$
+	26	29	NS
++	4	6	
+++	2	2	

*NS = Not significant.

Corometric FHR monitors and an I.L. pH and blood gas analyzer were used in the studies. The methods for analyzing FHR and measuring fetal scalp blood pH have been described previously.[1-3]

Babies in the trial were assessed at birth by means of the Apgar score, within 24 hours of birth by the pediatric resident, and by the appropriate pediatric consultant if there was any abnormality. Information was collected from the pediatric records by the research team. For healthy babies, assessment ceased at the time of discharge from hospital, which was a mean of 7 days. For abnormal babies, regular follow-up in the outpatient service was carried out. The brain-damaged babies had all been seen for at least 3 months, abnormal neurologic signs still being present. Analysis of the results was made with the aid of a computer

Table IV. Maternal analgesia

	Control	*Intensive care*	*Statistical test*
No. of narcotic injections			
0	16	21	$\chi^2 = 2.90$
1	93	81	NS*
2	52	52	
3	10	15	
4+	4	6	
Duration of epidural anesthesia (hr.)			
No.	43	50	$\chi^2 = 0.53$ NS
Mean	5.26	4.16	t = 1.11
S.D.	5.25	5.25	NS

*NS = Not significant.

Table V. Delivery

	Control	*Intensive care*	*Statistical test*
Cesarean section	24	39	$\chi^2 = 4.96$†
Assisted vaginal delivery	67	70	$\chi^2 = 0.05$ NS*
Difficult delivery			
Spontaneous	2	4	$\chi^2 = 0.61$
Forceps	5	0	NS
Cesarean section	1	0	

*NS = Not significant.
†$p < 0.05$.

Table VI. Common reasons for cesarean section

	Control	*Intensive care*	*Statistical test*
Failure to progress	13	16	$\chi^2 = 0.57$ NS*
Cephalopelvic disproportion	7	10	$\chi^2 = 0.00$ NS
Abnormal FHR	14	28	$\chi^2 = 1.83$ NS
Previous cesarean section	0	6	$\chi^2 = 6.06$†

*NS = Not significant.
†$p < 0.001$.

Table VII. Maternal infection

	Control	*Intensive care*	*Statistical test*
Intrapartum			
Obstetric	6	3	$\chi^2 = 1.50$
Nonobstetric	3	5	NS*
Postpartum			
Obstetric	47	49	$\chi^2 = 4.42$
Nonobstetric	6	15	NS

*NS = Not significant.

Table VIII. Neonate

	Control	*Intensive care*	*Statistical test*
Apgar score			
0-3	6	4	$\chi^2 = 1.00$
4-6	19	24	NS*
7-10	150	147	
Resuscitation at birth			
Nil	5	6	$\chi^2 = 4.65$
Routine suction and oxygen	115	131	NS
IV therapy and intubaton	55	37	
Neonatal intensive care	30	11	$\chi^2 = 8.95$†
Neurologic symptoms and signs	13	2	$\chi^2 = 10.03$†

*NS = Not significant.
†$p < 0.001$.

Table IX. Neonatal symptoms and signs

Symptoms and signs	*Control*	*Intensive care*
Twitching	9	2
Apneic episodes	8	—
Hypotonia	4	—
Convulsions	4	—
Tachypnea	3	—
High-pitched cry	3	—
Hypertonus	2	—

using appropriate statistical tests: the chi square, Student's t test, and analysis of variance.

Results

Comparability of control and intensive-care groups. The reasons for patients entering the trial are shown in Table I. Although the incidence of two abnormalities was different in the two groups ($p < 0.05$), analysis of fetal outcome in these cases demonstrated no prejudicial influence on the validity of the trial. The control and intensive-care groups were similar in respect to the mother's age and parity, the gestation at delivery, and the infant's birth weight (Table II); in particular, the number of babies weighing less than 2,500 grams was similar.

Mother. The control and intensive-care groups were similar in respect to the length of labor, the incidence of induction of labor, the induction–delivery interval, the incidence, maximum dose, and duration of oxytocin use, the incidence, volume, and duration of intravenous fluid use, and the incidence of ketonuria (Table III). The high induction rate (42 per cent) reflects the

Table X. Neonatal diagnoses

Diagnoses	*Control*	*Intensive care*
Brain damage	4	—
Perinatal hypoxia	3	1
Cerebral hypoxia/ irritation	2	—
Apnea/cyanotic attacks	2	—
Tachypnea	2	—
Uncertain	2	1
Hypoglycemia	1	—
Glucose-6-phosphate-dehydrogenase deficiency	1	—

Table XI. Neonate

	Control	*Intensive care*	*Statistical test*
Nursery care (days)			
No.	109	125	$\chi^2 = 2.90$ NS*
Mean	3.8	3.1	$t = 2.38$†
S.D.	2.5	2.0	
Gavage feeding (days)			
No.	32	24	$\chi^2 = 1.72$ NS
Mean	3.3	3.4	$t = 0.15$ NS
Incubator care (days)			
No.	77	85	$\chi^2 = 0.56$ NS
Mean	2.8	2.5	$t = 1.12$ NS
S.D.	2.2	1.9	
Neonatal infection (excluding "sticky-eye")	8	4	$\chi^2 = 0.78$ NS

*NS = Not significant.
†$p < 0.05$.

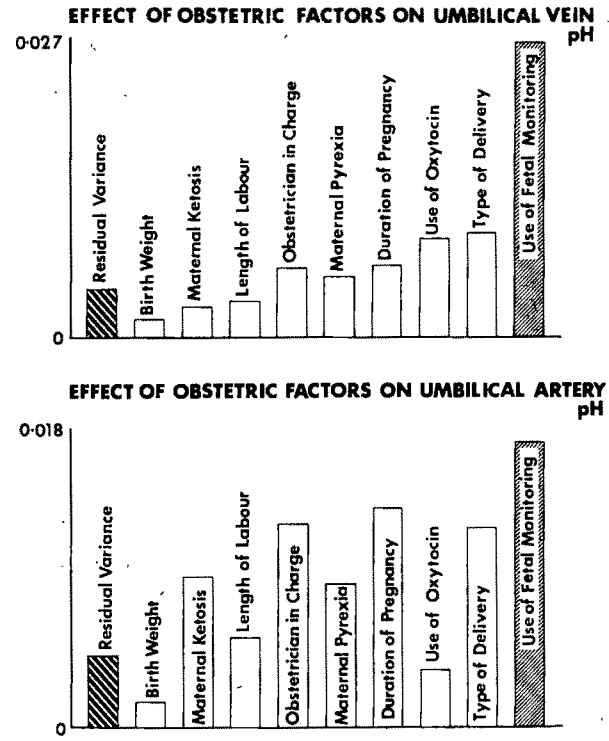


Fig. 1. The effects of various obstetric parameters on the variance of umbilical cord blood pH. The abscissa is the scale of variance and shows the relative importance of various parameters influencing changes in cord blood pH.

management of a group of patients with obstetric complications. The use of narcotics and epidural anesthetics also was similar in the two groups (Table IV).

More cesarean sections—39 (22.3 per cent) compared to 24 (13.7 per cent)—were done in the fetal intensive-care group (Table V). The only significant difference between the groups, when considering factors which may determine cesarean section, was the chance higher incidence of previous cesarean section in the intensive care group (Table VI). The cesarean section rate in the two groups was not significantly different after removing the six patients who had previous cesarean section, $\chi^2 = 1.70$ (Table V).

The occurrence of fewer difficult forceps deliveries in the fetal intensive-care group—none conpared to five (Table V)—was not statistically significant ($\chi^2 = 2.85$). However, the occurrence of five difficult forceps deliveries in the control group may be clinically important. It is possible that fetal intensive care may have indicated earlier that dystocia was adversely affecting the fetus, FHR being abnormal as a result of head compression or uterine overactivity. In these circumstances, cesarean section would be preferred.

The incidence of infection during or after labor was not significantly different in the two groups (Table VII).

Neonate. The Apgar scores and the incidence of resuscitation were not different in the two groups (Table VIII).

The number of babies requiring intensive care after admission to the nursery was higher in the control group (Table VIII). This care included the use of the incubator, intravenous therapy, assisted respiration, and correction of acid–base abnormalities.

Thirteen infants in the control group and only two in the intensive care group showed neurologic symptoms and/or signs (Table VIII). These symptoms and signs were not always serious (Table IX), but four babies in the control group were diagnosed as having brain damage (Table X). Perinatal hypoxia was thought to cause neurologic changes in several other babies.

During the trial there was one stillbirth and one neonatal death. The stillbirth was asphyxial, was in the control group, and may have been avoided by monitor-

Table XII. Umbilical cord blood analysis

	Control§			*Intensive care*			
	No.	*Mean*	*SD*	*No.*	*Mean*	*SD*	*t test*
Umbilical vein							
pH	37	7.313	0.055	50	7.349	0.075	2.44*
Po_2 (mm. Hg)	37	24.3	5.5	50	30.5	9.3	3.65‡
Pco_2 (mm. Hg)	37	43.9	8.8	50	37.9	9.1	3.13†
Umbilical artery							
pH	37	7.262	0.049	49	7.296	0.089	2.13*
Pco_2 (mm. Hg)	37	13.6	5.4	48	18.8	7.9	3.43‡
Pco_2 (mm. Hg)	37	54.8	10.3	49	47.2	11.1	3.28†

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.
§Measurements were restricted to patients delivered between 9.00 A.M. and 5.00 P.M.

Table XIII. Correlation of Apgar score with umbilical cord blood variable

Umbilical cord blood variable	*No.*	*Correlation coefficient*	*t test*
Umbilical vein			
pH	87	0.15	1.44 NS*
Po_2 (mm. Hg)	87	0.19	1.75 NS
Pco_2 (mm. Hg)	87	−0.24	2.24†
Umbilical artery			
pH	86	0.32	3.06‡
Po_2 (mm. Hg)	85	0.30	2.89‡
Pco_2 (mm. Hg)	86	−0.25	2.34†

*NS = Not significant.
†$p < 0.05$.
‡$p < 0.01$.

ing. The neonatal death was in the intensive-care group, was due to pulmonary hemorrhage a week after birth, and was thought to be unavoidable.

The babies from the control group spent longer in the nursery but the incidence of gavage feeding, incubator care, and neonatal infection was similar in the two groups (Table XI).

The pH, Po_2 and Pco_2 measurements in cord blood were significantly better in the intensive-care group than the control group (Table XII).

Apgar score and cord blood pH and gas measurements were significantly related; lower umbilical artery pH and Pco_2 were found more often when Apgar scores were low (Table XIII).

A variety of clinical factors which have been considered sometimes to influence fetal conditions were found not to affect cord blood pH and gas measurements. What was found most important in influencing cord blood pH, Po_2, and Pco_2 was the use of fetal intensive care (Figs. 1 through 3).

Comment

The removal of patients from the trial by one of the obstetricians reflects the difficulty in making ethical decisions concerning trials involving fetal welfare. However, the reasons justifying the present trial were: the ready and sometimes uncritical acceptance of new techniques in medicine, the controversy in our own hospital concerning the value of intensive care, the cost of providing intensive care, the difficulty in deciding the extent to which intensive care should be applied in obstetrics, and the possibility of intensive-care techniques being harmful rather than helpful. The trial was stopped when it became clear that intensive care was associated with improved neurologic and biochemical status of the neonate.

The improvement associated with intensive care may have resulted from the use of fetal diagnostic tests or from some other factor which inadvertently may have been associated with intensive care. It could be argued that patients being monitored in a labor ward also may have improved nursing and medical attention. However, this explanation seems unlikely. The obstetricians involved in the trial cared for both control and intensive-care patients, and the authors considered that while some were clinically more alert when caring for "high-risk" fetuses without the aid of intensive care, others were less attentive. Furthermore, members of the intensive-care team did not make clinical decisions, only provided the results of tests to obstetricians responsible for the clinical care of the patients.

What conclusions can be made from the differences found between the control and intensive-care groups? The occurrence of one asphyxial stillbirth and four brain-damaged infants in the control group is considered sufficient evidence to warrant the continuation of

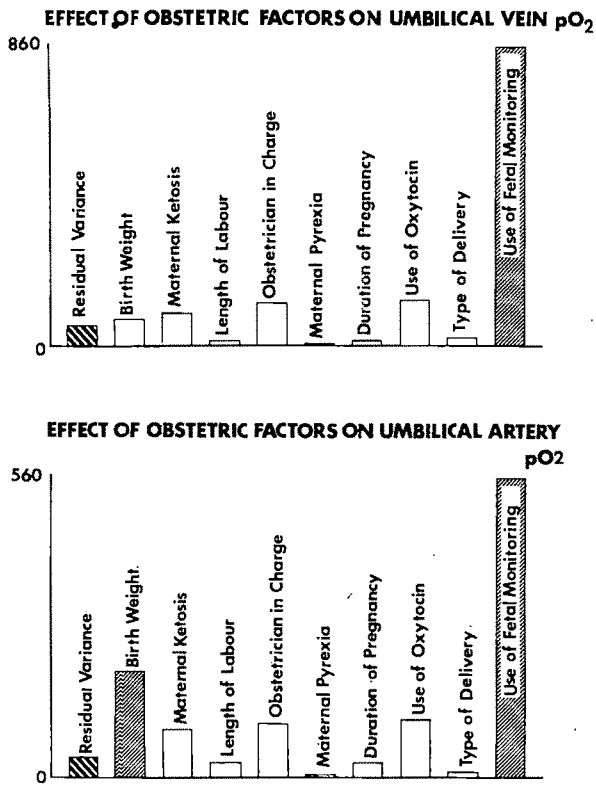


Fig. 2. The effects of various obstetric parameters on the variance of umbilical cord blood P_{O_2}. The abscissa is the scale of variance and shows the relative importance of various parameters influencing changes in cord blood P_{O_2}.

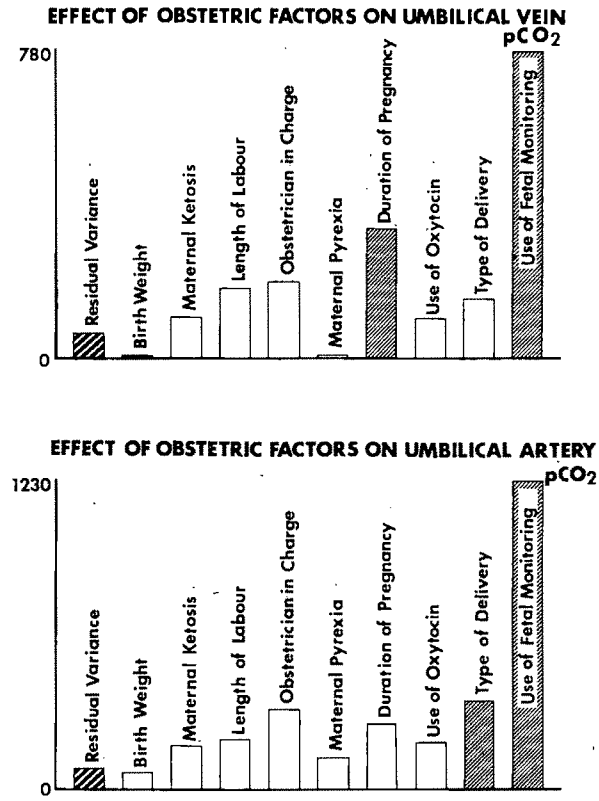


Fig. 3. The effects of various obstetric parameters on the variance of umbilical cord blood P_{CO_2}. The abscissa is the scale of variance and shows the relative importance of various parameters influencing changes in cord blood P_{CO_2}.

fetal intensive care in our own hospital. However, the results of this study may not apply elsewhere as the intensive-care unit personnel are experienced in the use of fetal diagnostic techniques, particularly in relation to the interpretation of FHR tracing and possible errors involved in measuring scalp blood pH.[4] The results of the current trial may discourage others from carrying out further controlled trials. Where financial support is readily available for fetal intensive care, such a view is reasonable as benefit is likely and techniques have little hazard for either the mother or fetus. However, in countries where funding of intensive care has to be considered in competition with other important medical needs, a controlled trial would appear justified to reaffirm and quantify the degree of benefit of intensive care to the fetus. In such a trial, monitoring of the control group would be beneficial because, should neurologic sequelae occur in some fetuses after birth, the appropriate FHR trace could be examined to see if it has prognostic value. It the present trial it was not possible to follow up babies in the two groups.

Because of the difficulty in organizing controlled trials and the detailed information available concerning fetuses studied in a trial, long-term follow-up of babies would be of interest. The importance of intrapartum FHR and fetal scalp blood pH changes in long-term follow-up of babies has yet to be determined.

The mother appears little influenced by fetal intensive care, the use of cesarean section and forceps and the incidence of intrauterine infection not being increased. No study of patients' emotional reaction was made in the trial and the possibility of both favorable and unfavorable reactions to intensive care remains. Many women suffer anxiety concerning the welfare of the fetus in utero and it seems likely that monitoring, properly explained to the patient, would reduce maternal anxiety concerning the fetus.

We wish to acknowledge the help of Sister J. Gaylard in particular and the medical and obstetric nursing staff of the Queen Victoria Memorial Hospital for their cooperation in carrying out this study.

REFERENCES

1. Renou, P., and Wood, C.: Interpretation of the continuous fetal heart rate record, *in* Beard, R. W., editor: Clinics in Obstetrics and Gynaecology, London, 1974, W.B. Saunders Company, Ltd., vol. 1, no. 1.
2. Lumley, J., Potter, M., Newman, W., Talbot, J. M., Wakefield, E., and Wood, C.: The unreliability of a single estimation of fetal scalp blood pH, J. Lab. Clin. Med. **77:** 535, 1971.
3. Lumley, J., McKinnon, L., and Wood, C.: Lack of agreement on normal values for fetal scalp blood, J. Obstet. Gynaecol. Br. Commonw. **78:** 13, 1971.
4. Wood, C., and Chang, A., editors: Studies in Perinatology, Melbourne, Australia, Monash University, Department of Obstetrics and Gynaecology, Queen Victoria Memorial Hospital.

A prerecorded program for the Ball pelvimetry technique

EMANUEL A. FRIEDMAN, M.D., MED.SC.D.

Boston, Massachusetts

Pelvimetry can be simplified by a recently devised computer program. The program can be used with any of several advanced programmable pocket or desk-top calculators. This approach is more accurate than either the nomogram or the slide rule, and demands much less time and attention.

THE X-RAY cephalopelvimetric technique first described in 1935 by Ball and Marchbanks[1] has several distinct advantages over other methods. It is capable of measuring the fetal head in any presenting position, providing a specific head volume in each case against which to judge the capacity of the pelvis based on measured dimensions. Moreover, it has essentially none of the technical drawbacks of other methods that require accurate positioning of the patient, precise placement of grids or rulings, or use of specially designed equipment. The geometric triangulation principles of the Ball technique have been previously outlined.[2] Detailed expositions of how the measurements are made from the x-ray films are also available[2, 3] and need not be repeated here.

Various aids have been introduced to simplify the mathematical manipulations needed to correct the film measurements for expected divergence error, to calculate the corresponding head volume and pelvic capacity, and to determine volume deficits where they exist. It is likely this useful clinical tool has not found greater acceptance among obstetricians and radiologists by virtue of the arithmetic involved. Nomograms[2, 4] and a special slide rule[5] have apparently not entirely resolved this problem. A recently devised computer program[6] has generated utilitarian tables that are proving to be most helpful in clinical practice at this institution. The sheer bulk of paper and the need to reduplicate the tables periodically as they deteriorate with use and time are the only obvious disadvantages we have encountered to date.

From the Department of Obstetrics and Gynecology, Beth Israel Hospital and Harvard Medical School.

Received for publication January 23, 1976.

Accepted March 10, 1976.

Reprint requests: Emanuel A. Friedman, M.D., Department of Obstetrics and Gynecology, Beth Israel Hospital, 330 Brookline Ave., Boston, Massachusetts 02215.

A computer program has now been evolved for use with any of several advanced programmable pocket or desk-top calculators. The 100-step sequence shown in Table I was written specifically for the HP-65* unit; it can be readily modified for other equipment. When the prerecorded magnetic card containing this program is inserted into the calculator, the operator can proceed to compute volumes, capacities, and deficits merely by entering the paired arrays of measured dimensions and object-film distances. As each pair is entered, the corrected volume is derived and stored for subsequent use in determining the deficit or for later reference purposes. In this program, subroutine A is used for entering the three important pelvic dimensions (widest transverse and anteroposterior diameters of the inlet and interspinous diameter at the midplane), and subroutine B for the two head circumference measurements (obtained from the anteroposterior and lateral films, respectively). All necessary corrections and conversions are automatically accomplished and the head volumes are averaged. After the five dimensions have been duly processed, subroutine C computes the deficits seriatim. To enter a new case, only the storage registers need to be cleared.

The flow of data is as follows: The first measured pelvic dimension (the widest transverse diameter of the inlet) is entered (key A) along with its object-film distance (key R/S). The data are automatically subprogrammed (subroutine E) for purposes of correcting the measured dimension for magnification distortion and beginning the computation of the corresponding volume

$$V = \frac{\pi D^3}{6}$$

The program returns to the point from which it had branched, there to complete the volume calculation and to seek an appropriate storage register. It tests

*Hewlett-Packard Company, Cupertino, California.

Table I. Programmed steps for Ball pelvimetry

LBLA	LBL1	LBLB	LBL2	LBLC	LBLE
ST08	RCL2	ST08	RCL5	RCL1	RCL8
E	1	2	RCL4	RCL6	R/S
×	+	ST07	+	−	ST06
ST03	ST08	E	2	R/S	gR↓
RCL1	gDSZ	ENT	÷	RCL2	100
1	RCL3	×	ST06	RCL6	ENT
+	RTN	÷	RCL5	−	ENT
ST08	RCL3	ST05	RTN	R/S	RCL6
gDSZ	ST02	RCL4		RCL3	−
GT01	RTN	1		RCL6	÷
RCL3		+		−	÷
ST01		ST08		RTN	RCL7
RTN		gDSZ			+
		GT02			3
		RCL5			gy^x
		ST04			6
		RTN			÷
					gπ
					RTN

each of the first three registers in turn and enters the derived volume into the first one it locates that contains no previously entered volume. Since this is the first entry, the capacity corresponding to the widest transverse inlet diameter would be stored in the first register. Next, a second dimension (the anteroposterior diameter of the inlet, key A) and its object-film distance (key R/S) are entered; the volume is computed and stored in the second register (subprogram 1). Entering the third pelvic dimension (interspinous diameter, key A) and its object-film distance (key R/S) complete the calculations of pelvic capacities as this volume is stored in the third register.

One of the measured head circumferences (from the anteroposterior film, key B) with its corresponding object-film distance (key R/S) is then entered, branched (subprogram E) for divergence correction, and further corrected for fetal scalp volume (by adding 2 cm. to the corrected cranial circumference). Initial computation of the head volume from the corrected circumference

$$V = \frac{C^3}{6\pi^2}$$

is undertaken, utilizing the steps shared in common with the calculation of volume from diameters. Returning to the point from which it branched, the program completes the volume calculation and proceeds to seek an appropriate storage register; the first head volume is stored in the fourth register. The remaining head circumference (from the lateral film, key B) and its object-film distance (key R/S) are handled in the same way, and the calculated volumes stored in the fifth register (subprogram 2). When both head volume storage registers are occupied, they are automatically averaged and the mean head volume stored in the sixth register. Finally, subprogram C determines the deficits between the mean head volume and the pelvic capacity as derived first from the widest transverse inlet diameter (key C), then from the anteroposterior inlet diameter (key R/S), and last from the interspinous diameter (key R/S again).

This approach is much more accurate than either the nomogram or the slide rule in clinical use. It is much less demanding in terms of time and attention than the aforementioned generated tables. The expense of a programmable calculator is offset by the advantages of the information it provides through the intermedium of this program, and of course by the many other uses to which it can be put.

REFERENCES

1. Ball, R. P., and Marchbanks, S. S.: Roentgen pelvimetry and fetal cephalometry: A new technique, Radiology **24:** 77, 1935.
2. Friedman, E. A., and Taylor, M. B.: A modified nomographic aid for x-ray cephalopelvimetry, Am. J. Obstet. Gynecol. **105:** 1110, 1969.
3. Ball, R. P.: Roentgenography: Pelycephalometry, *in* Glasser, O., editor: Medical Physics, Chicago, 1950, Year Book Medical Publishers, Inc., vol. II, p. 940.
4. Holmquest, H. J.: Nomogram for roentgenographic mensuration, Radiology **31:** 198, 1938.
5. Schwartz, G. S.: A simplified method of correcting roentgenographic measurement of the maternal pelvis and fetal skull, Am. J. Roentgenol. **71:** 115, 1954.
6. Klapholz, H.: A computerized aid to Ball pelvimetry, Am. J. Obstet. Gynecol. **121:** 1067, 1975.

Thief.



When baby takes more iron than mother can afford to give, *iron deficiency anemia of pregnancy* is a likely consequence.

Stolen iron can be replaced with a single formulation. **Tabron.**

Throughout pregnancy and the postpartum period, one Tabron tablet per day can usually fill her iron requirements. Tabron can also supply her with folic acid, a fecal softener, vitamin B_{12}, ascorbic acid, and other vitamins she's likely to need.

FILMSEAL®

Tabron®

a comprehensive hematinic... restores the iron and more

Each Tabron Filmseal represents: 304.2 mg ferrous fumarate (represents 100 mg of elemental iron); 500 mg ascorbic acid; 6 mg thiamine mononitrate; 6 mg riboflavin; 5 mg pyridoxine hydrochloride; 25 mcg cyanocobalamin, crystalline; 1 mg folic acid; 30 mg niacinamide; 10 mg calcium pantothenate; 30 I U vitamin E (*dl*-alpha tocopheryl acetate); 50 mg dioctyl sodium sulfosuccinate.

Caution: Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.

Photograph from "Behold Man" by Lennart Nilsson

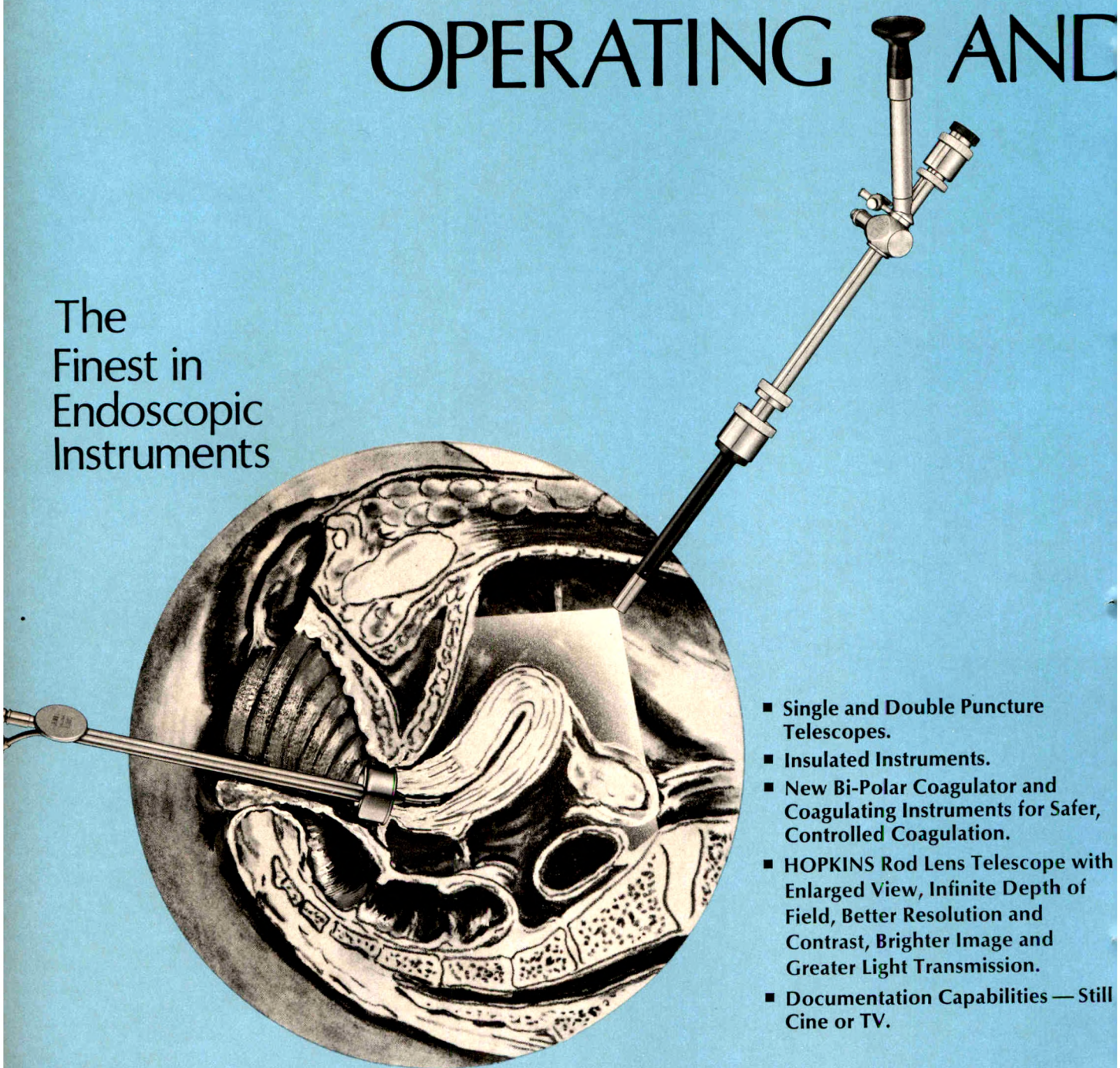
Parke, Davis & Company, Detroit, Michigan 48232

PARKE-DAVIS

PD-JA-0807-3-P (4-7

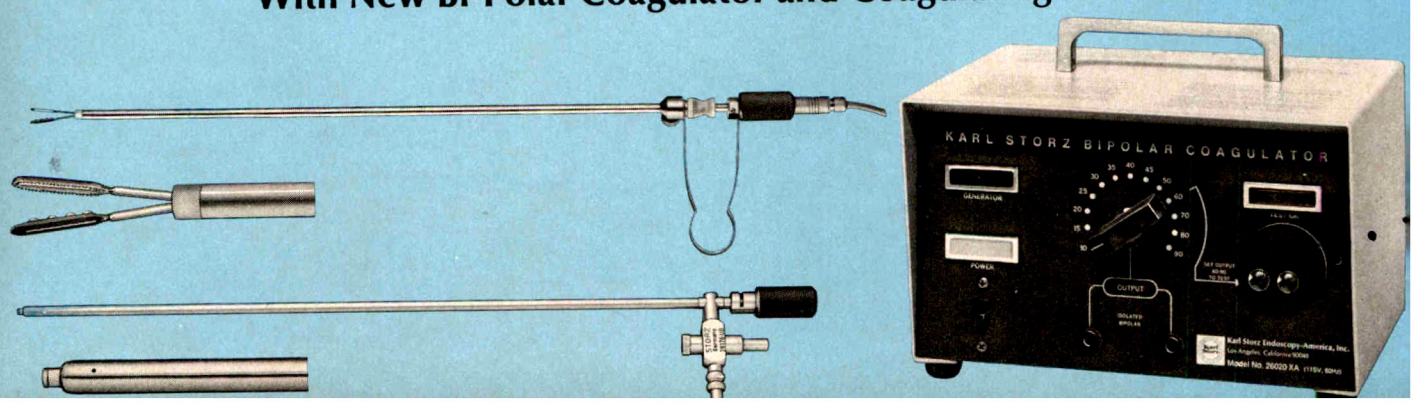
NEW LAPAROSCOPES! OPERATING AND

The Finest in Endoscopic Instruments

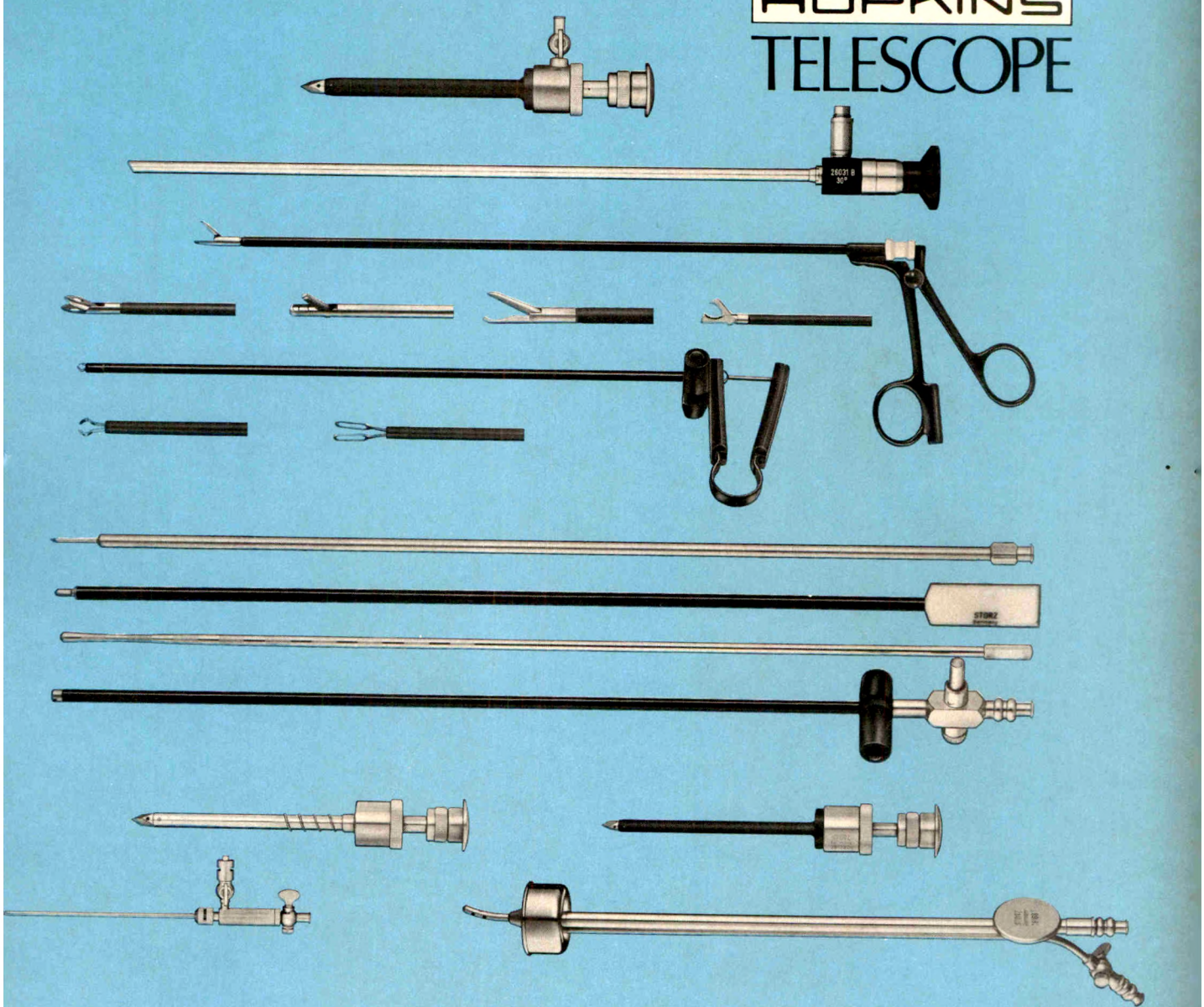


- Single and Double Puncture Telescopes.
- Insulated Instruments.
- New Bi-Polar Coagulator and Coagulating Instruments for Safer, Controlled Coagulation.
- HOPKINS Rod Lens Telescope with Enlarged View, Infinite Depth of Field, Better Resolution and Contrast, Brighter Image and Greater Light Transmission.
- Documentation Capabilities — Still Cine or TV.

With New Bi-Polar Coagulator and Coagulating Instruments



ENLARGED VIEW from Karl Storz with HOPKINS TELESCOPE



Karl Storz

Karl Storz Endoscopy—America, Inc.
658 South San Vicente Blvd., Los Angeles, Ca. 90048

FOR TOLL FREE SERVICE 800-421-0837
(Except California) In Calif. CALL (213) 651-1068

Gentlemen:

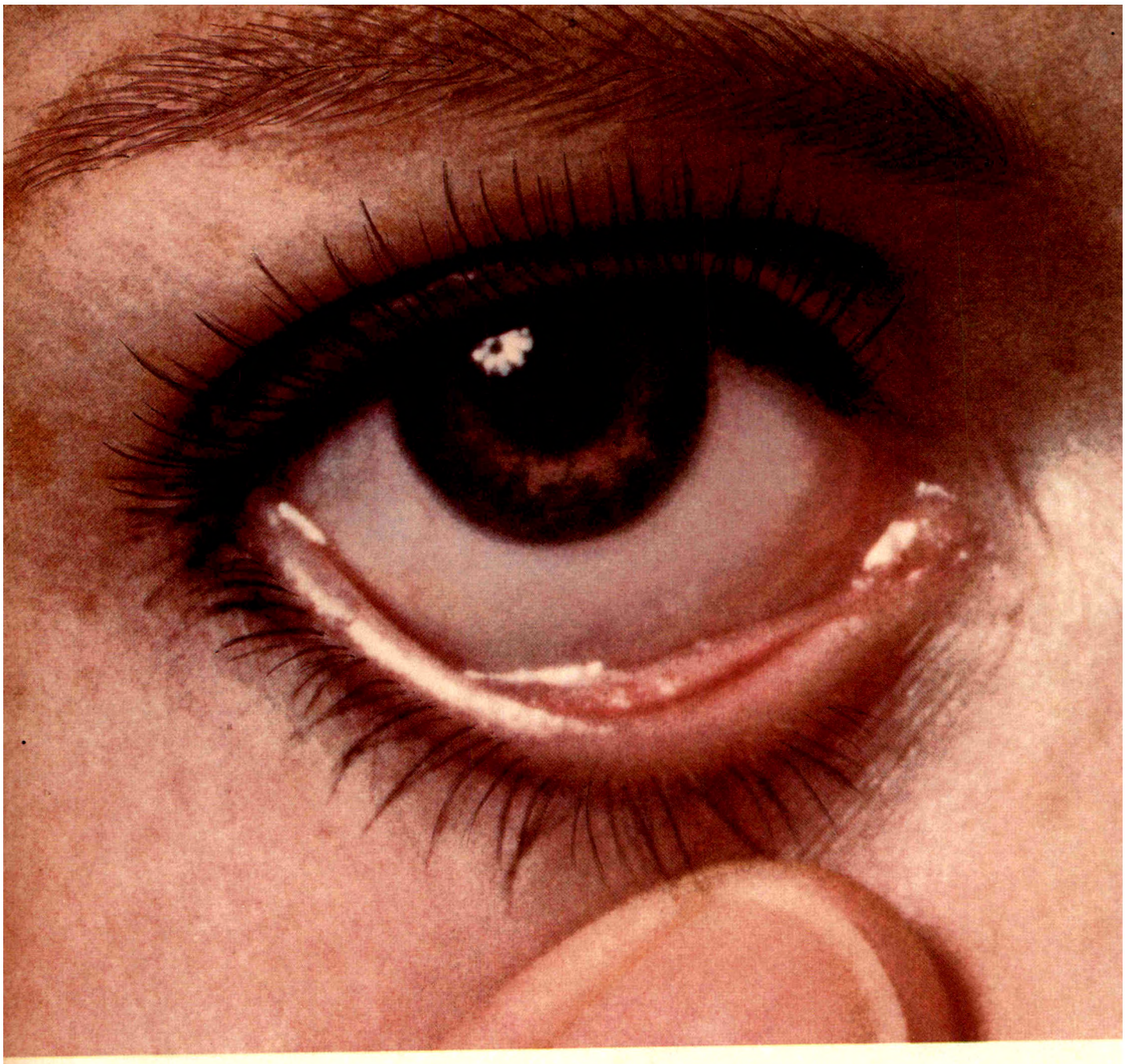
☐ Please send me latest brochure and prices. ☐ Please have a Karl Storz Representative phone me for an appointment.

Thank you.

Name (please print)

Address

City State Zip



Which hematinic works best? –the one that she takes.

Unfortunately, many women do not take their hematinics.

A majority of pregnant women fail to ingest oral iron supplements because of intolerance to oral iron and resistance to multiple daily dose regimens.*

By minimizing the chances of gastric upset and simplifying dosage (once-a-day), Abbott hematinics encourage compliance.

COMFORT—the Gradumet® controlled-release of iron takes place primarily in the small intestine where absorption of iron is greatest with minimal chance of gastric upset

COOPERATION—once-a-day dosage assures optimal patient acceptance.

CONVENIENCE—500 mg. of Vitamin C to enhance iron absorption is combined with iron and B-Complex in a single tablet.

6093160R1

Iberet®-500

Hematinic Supplying Controlled-Release Iron with Vitamin C and B-Complex (contains no folic acid)

*Kitay, D. Z., Contemporary Ob/Gyn, 2:17, 1973.

Iberet-Folic-500® ℞

Controlled-Release Iron with Vitamin C and B-Complex including Folic Acid

Please see opposite page for Brief Summary.

ABBOTT

Iberet®-500

One Filmtab® tablet a day supplies:

Controlled-Release Iron

Ferrous Sulfate,
(equivalent to
elemental iron—105 mg.) .. 525 mg.

Plus High Potency Vitamin C

Vitamin C
(as Sodium Ascorbate) .... 500 mg.

Plus the B-Complex
(contains no folic acid)

Niacinamide ..... 30 mg.
Calcium Pantothenate ..... 10 mg.
Vitamin B_1
(Thiamine Mononitrate)..... 6 mg.
Vitamin B_2 (Riboflavin) ..... 6 mg.
Vitamin B_6
(Pyridoxine Hydrochloride) .. 5 mg.
Vitamin B_{12}
(Cyanocobalamin) ..... 25 mcg.

INDICATIONS: For conditions in which iron deficiency occurs concomitantly with deficient intake or increased need for the B-complex vitamins (contains no folic acid).

Iberet-Folic-500® ℞

One Filmtab tablet a day supplies the same formula as Iberet-500 plus:

Folic Acid .....800 mcg.

INDICATIONS: In non-pregnant adults, for the treatment of iron deficiency and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins. Also indicated in pregnancy for the prevention and treatment of iron deficiency where there is a concomitant deficient intake or increased need for B-complex vitamins (including folic acid).

CONTRAINDICATION: Pernicious anemia.

WARNINGS: Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTION: Where anemia exists, its nature should be established and underlying causes determined. Iberet-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS: The likelihood of gastric intolerance is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

6093160

Gradumet®–Controlled-release dose form, Abbott.
Filmtab–Film-sealed tablets, Abbott.

ABBOTT

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 339, Erie, Pennsylvania 16512.

ASSISTANT PROFESSOR OF OBSTETRICS & GYNECOLOGY

The Charleston Division of the West Virginia University Medical Center is seeking applications for the position of Assistant Professor in the Department of Obstetrics and Gynecology. Applicant must be board certified, interested in medical students, housestaff, and other health profession training and education. A background of good clinical experiences with special interest in Ob-Gyn Endocrinology is preferable. Qualified and interested applicants should contact Narinder N. Sehgal, M.D., Director, Department of Ob/Gyn, Charleston Division, West Virginia University Medical Center, 3200 MacCorkle Avenue, S.E., Charleston, West Virginia 25304. An Equal Opportunity/Affirmative Action Employer M/F.

In serious respiratory tract infections*...

*due to indicated susceptible organisms



Until the cultures come back, 'ANCEF' offers:

• Broad coverage of major respiratory pathogens

Streptococcus pneumoniae (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

• High and prolonged serum levels

Single 1 gram IV injections in healthy adult volunteers produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.

• Convenient IV or IM administration at same dosage schedule

Serious respiratory tract infections usually require immediate treatment. In these cases, prudent medical judgment and the use of 'Ancef', when appropriate, can save valuable time while waiting for culture results.

When culture results return, if indicated organism is sensitive to 'Ancef'—and chances are it will be—therapy is already under way. If it isn't sensitive, then 'Ancef' should be discontinued and an appropriate antibiotic should be selected.

Injectable benzathine penicillin is considered the drug of choice in treatment and prevention of streptococcal infections, including prophylaxis of rheumatic fever.

Adverse Reactions

Reported adverse reactions include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions, please see next page.

Warning: In penicillin-sensitive patients, cephalosporins should be used cautiously because of evidence of cross-allergenicity of the penicillins and cephalosporins.

Please see next page for a brief summary of the prescribing information.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl) thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae (formerly *D. pneumoniae*)
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported.

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible Gram positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg. or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.
SK&F



Ortho-Novum 1/80 □ 21

Each tablet contains 1 mg norethindrone and 0.08 mg mestranol. TRADEMARK

a history of good patient acceptance

low incidence of breakthrough bleeding

Less than 2% overall experience in 3,464 women over 34,068 cycles.

low incidence of spotting

Less than 3% overall experience in 3,464 women over 34,068 cycles.

low dropout rate

Only 3.6% of women in clinical studies dropped out because of adverse reactions. Serious as well as minor conditions have been reported following the use of oral contraceptives. These conditions include thromboembolic disease. The physician should remain alert to the earliest manifestation of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

highly effective

Ortho-Novum 1/80 □ 21 is a highly effective, well-balanced oral contraceptive. Moreover, it is packaged in the unique, crush-proof DIALPAK*Tablet Dispenser to help reduce the chance of patient failure. Also available in a 28-day DIALPAK Tablet Dispenser.

See prescribing information on following page.

*TRADEMARK © OPC 1975

Ortho-Novum 1/80□21 and 28

TRADEMARK

Each white tablet contains 1 mg norethindrone and 0.08 mg mestranol.
Each green tablet in the 28-day regimen contains inert ingredients.

a history of good patient acceptance



Ortho-Novum 1/80□21 and Ortho-Novum 1/80□28

Description: Each white ORTHO-NOVUM 1/80 tablet contains 1 mg of the progestational substance, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol. Each green tablet in the 28-day regimen contains inert ingredients.

Actions: ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of contraceptives.

Precautions: 1. A thorough history and physical examination should be performed be prescribing oral contraceptives and periodically during their administration and sh include special reference to breasts and pelvic organs, including Papanicolaou smear s estrogens have been known to produce tumors, some of them malignant, in five speci subprimate animals. 2. Endocrine and possibly liver function tests may be affected by ment with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28. Therefore, if such are abnormal in a patient taking ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□ is recommended that they be repeated after the drug has been withdrawn for two monti Under the influence of estrogen-progestogen preparations, pre-existing uterine fibr mata may increase in size. 4. Because these agents may cause some degree of fluid tion, conditions which might be influenced by this factor, such as epilepsy, migr asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough b ing, and in all cases of irregular bleeding per vaginam, nonfunctional causes shoul borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measure indicated. 6. Patients with a history of psychic depression should be carefully observec the drug discontinued if the depression recurs to a serious degree. 7. Any possible influ of prolonged ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy on pitu ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glu tolerance has been observed in a significant percentage of patients on oral contracep The mechanism of this decrease is obscure. For this reason, diabetic patients shou carefully observed while receiving ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/8 therapy. 9. The age of the patient constitutes no absolute limiting factor, although trea with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 may mask the onset climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/80□ ORTHO-NOVUM 1/80□28 therapy when relevant specimens are submitted. 11. Sus ble women may experience an increase in blood pressure following administration traceptive steroids. 12. Cholestatic jaundice has been reported in users o contraceptives. If this occurs ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/8 should be discontinued. This condition is more likely to occur in patients who experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic dice of pregnancy should be carefully observed during ORTHO-NOVUM 1/80□ ORTHO-NOVUM 1/80□28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statis significant association has been demonstrated between use of oral contraceptives ar following serious adverse reactions: thrombophlebitis, pulmonary embolism, cer thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has neither confirmed nor refuted for the following serious adverse reactions: neuro- lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral cont tives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and ing), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea durin after treatment, edema, chloasma or melasma, which may persist, cholestatic jau migraine, rash (allergic), mental depression, change in weight (increase or decr breast changes (tenderness, enlargement and secretion), changes in cervical erosic cervical secretions, suppression of lactation when given immediately post-partum, blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral con tives, an association has been neither confirmed nor refuted: anovulation post-trea which tends to occur more frequently in women with a history of menstrual dis premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syn headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, ism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eru itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: function—increased sulfobromophthalein retention and other tests; coagulation increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; incre platelet aggregability; thyroid function—increase in PBI, and butanol extractable bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol det tion.

References: **1.** Royal College of General Practitioners: Oral Contraception and Th Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Em in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.F R.: Investigation of Relation between Use of Oral Contraceptives and Thromboe Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Mas Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptiv Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Or traception and Increased Risk of Cerebral Ischemia or Thrombosis. N Engl *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young W Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contrac and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Diseas Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programm cet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Cor tives and Health, 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glob Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:1: July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patier Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health 62 685, May 1972. **11.** Mann, J.I.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial In in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J 245, May 3, 1975. **12.** Mann, J.I.; Inman, W.H.W.: Oral Contraceptives and Dea Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J. J.; Nora, A. H Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Med *291*(14):697-700, Oct. 3, 1974.

OJ 719-5R

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

FETUS, PLACENTA, AND NEWBORN

Sonar biparietal diameter

I. Analysis of percentile growth differences in two normal populations using same methodology

RUDY E. SABBAGHA, M.D.
FRANCA B. BARTON, M.S.
BRUCE A. BARTON, M.S.
Chicago, Illinois, and Pittsburgh, Pennsylvania

BPD measurements were obtained from 107 white and 91 black normal gravid women, with established dates, between weeks 16 to 40 of pregnancy. The sonar methodology used is uniform, employing nonpersistent image scanning with electronic calipers. It is noted that the BPD percentile growth patterns derived from these racially different fetuses are alike. Similarly, the fetal age distributions corresponding to white vs. black fetal BPD's show minor differences. From a clinical standpoint, therefore, one percentile curve is constructed for both populations. It is concluded that the BPD differences observed in the currently used growth curves, reported by different investigators, are related to nonuniformity in sonar BPD methodology.

IN THE EMERGING field of perinatal medicine, it is necessary to evaluate the cephalic growth pattern of a particular fetus along a defined and narrow percentile range rather than in comparison to a standardized norm, or a mean value ±2 S.D. A more precise assessment of abnormal growth is possible if the percentile range of the biparietal diameter (BPD) is known for each week of gestation. This paper presents the normal sonar BPD percentile values from 16 to 40 weeks of pregnancy for two fetal populations.

From the Departments of Obstetrics and Gynecology of Northwestern University–Prentice Women's Hospital and The University of Pittsburgh–Magee Women's Hospital.

Received for publication June 25, 1975.

Revised April 13, 1976.

Accepted May 10, 1976.

Reprint requests: Rudy E. Sabbagha, M.D., Department of Obstetrics and Gynecology, Northwestern University–Prentice Women's Hospital, Chicago, Illinois 60611.

Materials and methods

A total of 198 parturients of similar socioeconomic status had serial cephalometry performed from 16 weeks of pregnancy through term. Of these women there were 107 white and 91 black gravidas. The sonar BPD was measured from the B-scan tracing of the fetal head with the technique of nonpersistent image scanning with electronic calipers as described by Sabbagha and Turner[1] and Sabbagha.[2] The BPD caliper readings were accepted only if they fell within 1 mm. of the B-scan picture. The ultrasound tissue velocity used was 1,540 meters per second. The sonar equipment utilized in the study was internally calibrated, so that the electronically displayed marker scale correlated precisely with both the display graticule and the calipers. In addition, the linearity, depth, and horizontal as well as vertical tracking of the system were checked by a portable water-filled circular phantom with wire depth markers placed at 4 cm. intervals.

The patients in the study fullfilled all the following

Table I. Observed BPD values

Scans	*Weeks*	*BPD*
First	35 – 3*	8.4
Second	37 – 3	8.6
Third	39 – 3	8.8

*–3 = less 3 days.

Table II. Final BPD values

Weeks	*BPD*
35	8.44
36	8.54
37	8.64
38	8.74
39	8.80

criteria: (1) the pregnancy was uncomplicated; (2) the dates were established by (a) a known last menstrual period (LMP) and (b) spontaneous delivery ±2 weeks of the menstrual estimated date of delivery (EDD); (3) the delivery of a normal term neonate.[3] Adherence to these strict conditions was necessary so that the dates would be unequivocally correct and the fetal population would as nearly as possible approach normalcy, thus resulting in the construction of a meaningful percentile growth curve.

The serial BPD values for each fetus were plotted to show the normal weekly growth pattern. In addition, interpolation was used to show the expected BPD's between two already established sonar readings. The interval between the latter sonar scans was by definition less than 4 weeks apart in the gestational period of 16 to 28 weeks, and not more than 2 weeks apart between 28 and 40 weeks of pregnancy in accordance with the biologic assumption of nearly linear growth over short intervals of time. Additionally, extrapolation to either end of the curve was carefully avoided because of the well-recognized changes in slope encountered at the ends of any growth curve. Use of this statistical methodology resulted in the maximum use of the available data with almost no loss in accuracy. For example, if a fetus were to have the observed BPD values shown in Table I, interpolation would be made at the thirty-sixth and the thirty-eighth whole-week points and would have values of 8.54 and 8.74 cm., respectively. The BPD at week 37 would carry the value interpolated between weeks 37 – 3* and 39 – 3. Finally, the first and the third scan readings were applied to the nearest whole-week points, thus avoiding any unknown errors due to extrapolation. In the example cited above the final values for the case would be as shown in Table II.

*–3 = Less 3 days.

Table III. Fetal age percentile values for BPD's of black and white fetuses from 3.5 to 9.5 cm.*

	*Fetal age percentiles (wk.)**						
BPD	*5*	*10*	*25*	*50*	*75*	*80*	*95*
3.5	17+	17	16+	16	16–	16–	15+
3.6	18	17+	17	16+	16	16	15+
3.7	19	18	18	17–	16	16	16
3.8	19	18+	18+	17	16+	16+	16
3.9	19+	19	18+	17+	17–	17–	16
4.0	19+	19	19–	18–	17	17–	16
4.1	19+	19	19–	18	17+	17+	16
4.2	20–	19+	19	18+	17+	17+	16+
4.3	20	20–	19+	19–	18–	18–	17–
4.4	20+	20	20–	19	18+	18	17
4.5	21–	20+	20	19+	19–	18	17+
4.6	21	21–	20+	20–	19	18+	18–
4.7	21+	21	21–	20	19+	19	18
4.8	21+	21	21	20+	20–	19+	18–
4.9	22–	21+	21+	21–	20	19+	19–
5.0	22	22	22–	21	20+	20–	19
5.1	22+	22	22–	21+	20+	20	19+
5.2	23–	22+	22	22–	21–	20+	20–
5.3	23	23–	22+	22–	21	21–	20
5.4	24–	23+	23–	22	21+	21+	20+
5.5	24	24–	23	22+	22–	21+	21–
5.6	24	24–	23+	23–	22	22–	21
5.7	24+	24	24–	23	22+	22+	21+
5.8	25–	24+	24	23+	23–	23–	21+
5.9	25	25–	24+	24–	23	23–	22–
6.0	25+	25	25–	24	23	23	22–
6.1	26–	25+	25	24+	23+	23+	22
6.2	26	26–	25+	25–	24–	23+	22+
6.3	26+	26	26–	25	24	24	23–
6.4	27–	26+	26	25+	24+	24+	23–
6.5	27+	27	26+	26–	25	25	24–
6.6	28–	27+	27–	26	25+	25+	24–
6.7	28	28–	27	26+	26–	26–	24
6.8	28+	28	27+	27–	26	26–	24+
6.9	29	28+	28–	27	26+	26+	25–
7.0	29+	29–	28	27+	27–	26+	25–
7.1	30	30–	28+	28–	27	27–	25+
7.2	31–	30–	29–	28–	27+	27	25+
7.3	31	30	29	28	28–	27+	26–
7.4	32–	31	29+	28+	28–	27+	26
7.5	32	32–	30–	29–	28+	28–	26+
7.6	33–	32	30	29	28+	28	27–
7.7	33	32	30+	30–	29–	28+	27
7.8	33	32+	31–	30	29–	29–	27+
7.9	33+	33	31+	30+	29	29	28–
8.0	34	33+	32	31–	29+	29+	28
8.1	34+	34	32+	31	30–	30–	28+
8.2	35	35–	33–	31+	30	30	29–
8.3	36–	35	33	32	31	30+	29
8.4	36	36–	33+	32+	31	31–	29
8.5	36+	36–	34–	33	31+	31	29+
8.6	36+	36–	34	33+	31+	31	29+
8.7	37–	36	35–	34	32–	31+	30–
8.8	37	36+	35+	34+	32	32–	30
8.9	38–	37	36	35+	33	32+	31
9.0	38+	37+	37–	36–	33+	33	32–
9.1	39–	38	37	36+	34	34	32+
9.2	39	39–	37+	36+	35	35	33
9.3	39+	39–	38–	37–	35	35	34–
9.4	40–	39	38	37	36–	35	34+
9.5	40	39+	38+	37+	36	35	35–

*+ = 1 to 3 days; – = 1 to 3 days.

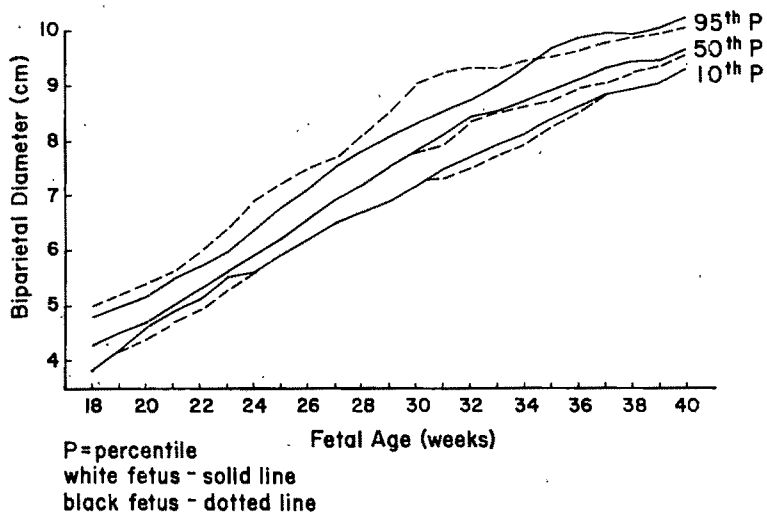


Fig. 1. Growth curves for black vs. white fetuses are similar except at the ninety-fifth percentile level.

Three observations became five, only the last value of which was slightly conservative, but this was offset by other cases which had their last BPD reading at the thirty-ninth whole-week point.

Percentile BPD values were then obtained for each week between pregnancy weeks 16 to 40, according to the method of Herrera.[4] In addition, the data was analyzed separately for black and Caucasian fetuses so that for each BPD reading from 3.7 to 9.5 cm. the percentile range of weeks of gestation was derived, again as outlined by Herrera.[4] Linear regression was not utilized because the serial nature of the BPD readings was in direct violation of one of the assumptions necessary for its use. The fetal age distribution for black fetal BPD's was only slightly greater than that for white fetuses. As a result, one table (Table III) was constructed to represent the gestational ages for both fetal populations.

Results

The BPD percentile measurements corresponding to different weeks of gestation for both black and white fetuses are shown in Table IV. In Fig. 1 are depicted the BPD differences between the two populations at the tenth, fiftieth, and ninety-fifth percentile levels. It is observed (Fig. 1, Table V) that these differences are very small, particularly below the ninety-fifth percentile rank. It is therefore advantageous for clinical monitoring purposes to combine the BPD growth patterns for the two racially heterogenous groups into one growth curve, as seen in Fig. 2. Similarly, the fetal age distributions for each specific BPD for both black and white fetuses are shown combined in Fig. 3 and Table III. It is noted that the maximal deviation of ±10 or 11 days for each BPD reading before week 26 reported in this study is almost identical to the results obtained by employing linear regression as previously reported by Sabbagha and associates.[5]

Table IV. BPD percentile value from 16 to 40 weeks for black and white fetuses

Fetal age (wk.)	*BPD percentiles*							*N*
	5	*10*	*25*	*50*	*75*	*80*	*95*	
16	3.1	3.2	3.4	3.7	4.0	4.1	4.5	12
17	3.4	3.5	3.7	4.0	4.3	4.4	4.7	15
18	3.7	3.8	4.0	4.3	4.5	4.6	4.9	22
19	3.9	4.2	4.3	4.5	4.8	4.9	5.1	33
20	4.2	4.5	4.6	4.7	5.0	5.1	5.3	39
21	4.5	4.8	4.9	5.0	5.3	5.4	5.5	40
22	4.9	5.0	5.2	5.3	5.6	5.7	5.8	48
23	5.2	5.3	5.5	5.6	5.9	6.0	6.2	57
24	5.5	5.6	5.8	5.9	6.2	6.3	6.6	50
25	5.8	5.9	6.0	6.2	6.5	6.6	7.0	47
26	6.1	6.2	6.3	6.6	6.8	6.9	7.3	43
27	6.4	6.5	6.7	6.9	7.1	7.2	7.6	51
28	6.6	6.7	7.0	7.2	7.4	7.5	7.9	51
29	6.8	6.9	7.3	7.5	7.8	7.9	8.3	53
30	7.1	7.2	7.6	7.8	8.0	8.2	8.6	50
31	7.3	7.4	7.8	8.0	8.2	8.4	8.8	48
32	7.5	7.6	8.0	8.3	8.4	8.6	9.0	47
33	7.7	7.8	8.3	8.5	8.6	8.8	9.1	50
34	7.9	8.0	8.5	8.7	8.9	9.1	9.3	50
35	8.2	8.3	8.7	8.8	9.1	9.3	9.6	49
36	8.3	8.5	8.9	9.0	9.3	9.4	9.7	48
37	8.4	8.8	9.0	9.2	9.4	9.5	9.8	43
38	8.5	8.9	9.1	9.3	9.5	9.6	9.9	42
39	8.7	9.0	9.2	9.4	9.6	9.7	10.0	29
40	8.9	9.3	9.4	9.5	9.7	9.8	10.1	15

Comment

Ninety-one black and 107 white fetuses, with well-established gestational ages, had BPD measurements for the purpose of comparing their growth pattern. The sonar methodology used was uniform, employing

Table V. Population differences of sonar BPD's (in percentiles) for black vs. white fetuses

Fetal age (wk.)	*Percentiles*											
	10			*25*			*50*			*75*		
	W	*W&B*	*B*	*W*	*W&B*	*B*	*W*	*W&B*	*B*	*W*	*W&B*	*B*
18	3.8	3.8	3.8	4.0	4.0	4.0	4.3	4.3	4.3	4.5	4.5	4.5
19	4.2	4.2	4.2	4.3	4.3	4.3	4.5	4.5	4.5	4.8	4.8	4.8
20	4.4	4.5	4.6	4.6	4.6	4.6	4.7	4.7	4.7	5.0	5.0	5.0
21	4.7	4.8	4.9	4.9	4.9	4.9	5.0	5.0	5.0	5.4	5.3	5.5
22	4.9	5.0	5.1	5.2	5.2	5.2	5.3	5.3	5.3	5.6	5.6	5.7
23	5.3	5.4	5.5	5.6	5.5	5.5	5.6	5.6	5.6	5.9	5.9	6.0
24	5.6	5.6	5.6	5.8	5.8	5.8	5.9	5.9	5.9	6.2	6.2	6.3
25	5.9	5.9	5.9	6.1	6.0	5.9	6.2	6.2	6.2	6.5	6.5	6.5
26	6.2	6.2	6.2	6.3	6.3	6.3	6.6	6.6	6.6	6.9	6.8	6.7
27	6.5	6.5	6.5	6.7	6.7	6.7	6.9	6.9	6.9	7.1	7.1	7.1
28	6.7	6.7	6.7	7.1	7.0	6.9	7.2	7.2	7.2	7.4	7.4	7.4
29	6.9	6.9	6.9	7.4	7.3	7.2	7.5	7.5	7.5	7.9	7.8	7.7
30	7.2	7.2	7.2	7.7	7.6	7.5	7.8	7.8	7.8	8.0	8.0	8.0
31	7.5	7.4	7.3	7.9	7.8	7.7	8.1	8.0	7.9	8.2	8.2	8.2
32	7.7	7.6	7.5	8.1	8.0	7.9	8.4	8.3	8.3	8.4	8.4	8.4
33	7.9	7.8	7.7	8.4	8.3	8.2	8.5	8.5	8.5	8.6	8.6	8.6
34	8.1	8.0	7.9	8.6	8.5	8.4	8.7	8.7	8.6	8.9	8.9	8.8
35	8.4	8.3	8.2	8.8	8.7	8.6	8.9	8.8	8.8	9.1	9.1	9.1
36	8.6	8.5	8.4	9.0	8.9	9.1	9.0	9.0	8.9	9.3	9.3	9.3
37	8.8	8.8	8.8	9.1	9.0	8.9	9.3	9.2	9.0	9.5	9.4	9.3
38	8.9	8.9	8.9	9.1	9.1	9.1	9.4	9.3	9.2	9.6	9.5	9.5
39	9.0	9.0	9.0	9.2	9.2	9.2	9.4	9.4	9.3	9.7	9.6	9.5
40	9.3	9.3	9.3	9.4	9.4	9.4	9.6	9.5	9.5	9.9	9.7	9.5

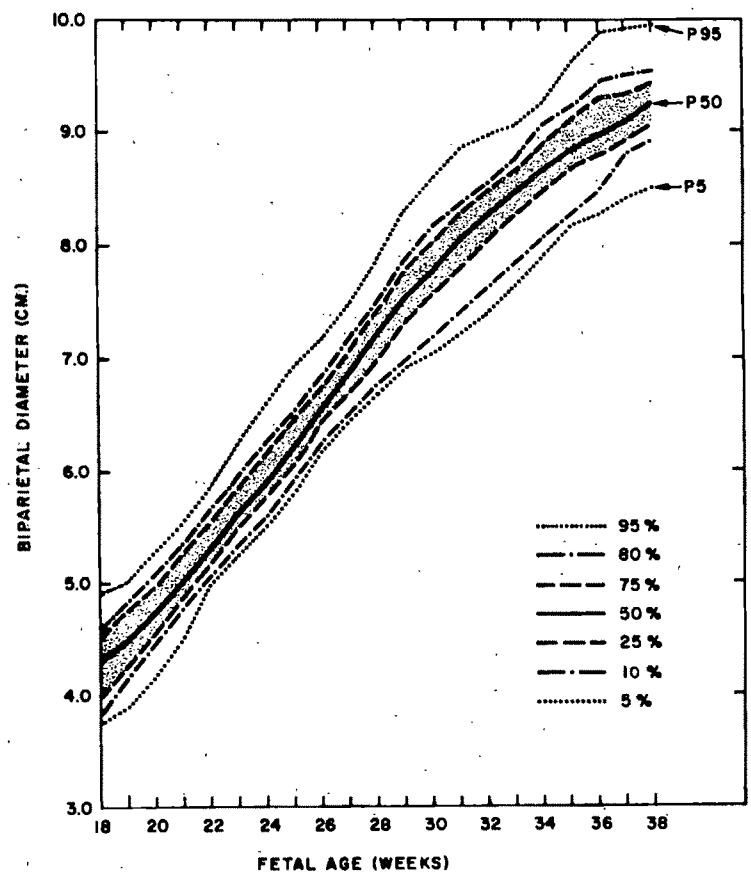


Fig. 2. Diameters of black and white fetuses.

95			N	
W	W&B	B	W	B
4.8	4.9	5.0	13	9
5.0	5.1	5.2	23	10
5.2	5.3	5.4	27	12
5.5	5.5	5.6	26	14
5.7	5.8	6.0	28	20
6.0	6.2	6.4	34	23
6.4	6.6	6.9	27	23
6.8	7.0	7.2	18	29
7.1	7.3	7.5	22	21
7.5	7.6	7.7	29	22
7.8	7.9	8.1	28	23
8.1	8.3	8.5	26	27
8.3	8.6	9.0	24	26
8.5	8.8	9.2	27	21
8.7	9.0	9.3	17	30
9.0	9.1	9.3	17	33
9.3	9.3	9.4	17	33
9.6	9.6	9.5	16	33
9.7	9.7	9.6	21	27
9.8	9.8	9.7	19	24
9.9	9.9	9.8	23	19
10	10	9.9	15	14
10.2	10.2		8	7

nonpersistent image scanning with electronic calipers. It is noted that the growth curves for these racially different fetuses, except at the ninety-fifth percentile ranking, are alike—showing only small differences of up to 2 mm. after 30 weeks of pregnancy. At the ninety-fifth percentile level, however, the black fetal BPD's are more than 2 mm. larger than the white fetal BPD's between pregnancy weeks 23 to 25 and 29 to 32. These differences at the ninety-fifth percentile level, although of uncertain etiology, are more likely to represent racial characteristics because the BPD measuring technique in both series is uniform.

From a clinical point of view the observed fetal racial BPD differences are not large enough to warrant the use of two separate growth curves. Therefore, the biparietal diameter weekly increments representing the two fetal populations are shown combined in Fig. 2 and Table IV. Similarly, the fetal age distribution for both the white and black fetuses is shown in Fig. 3 and Table III.

In estimating fetal age, sonographers rely on the mean BPD values attained at different weeks of gestation. Table VI show the BPD readings corresponding to 12 weekly intervals as reported by four investigators.[6] It is seen that the BPD values derived by Campbell and Newman[7] are remarkably similar to the data of this report. The technique of nonpersistent image scanning with electronic calipers is used by both

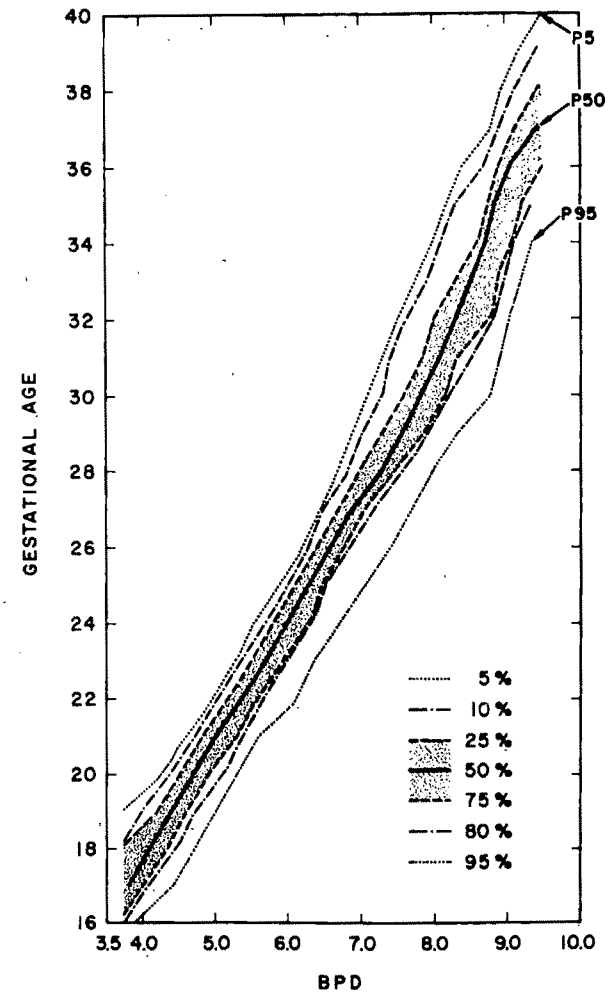


Fig. 3. Note the variation in gestational age for different BPD's (black and white fetuses).

Campbell and Sabbagha. The obvious conclusion: BPD population differences are indeed minimal when sonar methodology is uniform.

In comparison, Levi's BPD data are 4 to 10 mm. smaller than the author's BPD figures (Table VI). The result: a 1 to 5 week lag in fetal maturity estimates.

Flamme's[8] fiftieth percentile BPD data, however (Table VI), are only slightly smaller than the values reported in this study. Furthermore, Flamme's data reflect uniform progressive weekly growth increments. In contrast, Sanders' BPD readings fail to reflect such uniformity; for example, whereas his data show no growth during weekly intervals 24 to 26 and 30 to 32, he reported BPD increments of 1 cm. between pregnancy weeks 20 to 22 and 26 to 28; the corresponding weekly increases noted in most BPD growth charts are 6 and 6 mm., respectively. In addition, Sanders' and Sabbagha's BPD data obtained from similar black populations show disturbing differences: there is a lag

Table VI. BPD values vs. fetal age, as reported by five investigators

Weeks' gestation	*BPD's (cm.)*					
	Levi[6]	*Flamme*[8]	*Sabbagha: white population*	*Campbell*[7]*: *white population*	*Sabbagha: black population*	*Sanders*[6]*: *black population*
18	3.7	—	4.3	4.20	4.3	4.0
20	4.4	4.3	4.7	4.80	4.7	4.4
22	5.1	5.1	5.3	5.46	5.3	5.4
24	5.6	5.8	5.9	6.20	5.9	6.0
26	6.0	6.4	6.6	6.70	6.6	5.9
28	6.5	7.0	7.2	7.30	7.2	6.9
30	6.9	7.4	7.8	7.82	7.8	7.8
32	7.2	8.0	8.4	8.26	8.3	7.8
34	7.7	8.4	8.7	8.66	8.7	8.1
36	8.3	8.6	9.1	9.00	8.9	8.3
38	8.9	9.0	9.4	9.37	9.2	8.8
40	—	9.2	9.6	9.44	9.5	9.3

*Figures are reduced by factor of 1,540/1,600.

in the fetal maturity estimate of 2, 2, 3, and 4 weeks at pregnancy weeks 26, 32, 34, and 36, respectively. These differences can only be related to nonuniformity in sonar methodology.

REFERENCES

1. Sabbagha, R. E., and Turner, J. H.: Methodology of B-scan sonar cephalometry with electronic calipers and correlation with fetal birth weight, Obstet. Gynecol. **40:** 74, 1972.
2. Sabbagha, R. E.: Methodology of B-scan sonar cephalometry with electronic calipers and correlation with fetal birth weight. J. Clin. Ultrasound **1:** 68, 197.
3. Usher, R., MacLean, F., and Scott, K.: Pediatr. Clin. North Am. **12:** 835, 1965.
4. Herrera, L.: J. Lab. Clin. Med. **52:** 34, 1958.
5. Sabbagha, R. E., Turner, J. H., Rockett, H., et al.: Sonar BPD and fetal age: Definition of the relationship, Obstet. Gynecol. **43:** 7, 1974.
6. Sanders, R. L., and Conrad, M. R.: Radiol. Clin. North Am. **13:** 435, 1975.
7. Campbell, S., and Newman, G. B.: Growth of the fetal biparietal diameter during normal pregnancy, J. Obstet. Gynaecol. Br. Commonw. **78:** 513, 1971.
8. Flamme, P.: Br. Med. J. **3:** 384, 1972.

Sonar biparietal diameter

II. Predictive of three fetal growth patterns leading to a closer assessment of gestational age and neonatal weight

RUDY E. SABBAGHA, M.D.
BRUCE A. BARTON, M.S.
FRANCA B. BARTON, M.S.
ELAINE KINGAS, M.D.
JULIE ORGILL, A.S.U.T.S.
J. HOWARD TURNER, Sc.D.
Chicago, Illinois, and Pittsburgh, Pennsylvania

Serial BPD readings were obtained from 142 normal parturients, with established dates, between 20 to 40 weeks of pregnancy. It is noted that fetal BPD's can be separated into one of three percentile rankings: large (i.e. above the seventy-fifth percentile), average (i.e., twenty-fifth to seventy-fifth percentile), and small (i.e. below the twenty-fifth percentile). In addition, it is shown that, under normal conditions, fetuses initially placed in any one of these cephalic levels will continue to grow within the confines of the same percentile range. This biologic phenomenon has not been previously reported in human fetal growth. It is important because it leads to a closer prediction of fetal age and a better assessment of neonatal weight and outcome.

RECENTLY, Sabbagha and associates[1] reported that monkey fetuses of the same age when subgrouped, according to their BPD measurements, into four percentile divisions (tenth to twenty-fourth, twenty-fifth to forty-ninth, fiftieth to seventy-fourth, and seventy-fifth to ninetieth) will continue to grow, under normal condition, within the confines of their initially assigned ranges. This biologic phenomenon is of significance because it leads to both a predictable cranial growth rate, for each of the subgroups, and to an earlier more precise detection of abnormal deviations from the expected normal growth pattern; specifically, it may enhance the fetal diagnosis of entities such as hydrocephaly, microcephaly, and intrauterine failure to thrive.

From the Departments of Obstetrics and Gynecology of Northwestern University–Prentice Women's Hospital and the University of Pittsburgh–Magee Women's Hospital.

Received for publication April 13, 1976.

Accepted May 10, 1976.

Reprint requests: Rudy E. Sabbagha, M.D., Department of Obstetrics and Gynecology, Northwestern University–Prentice Women's Hospital, Chicago, Illinois 60611.

This paper presents the results of a longitudinal sonar study of the growth of the human fetus along percentile subgroupings. A marked similarity in the growth pattern is noted between both the human and the rhesus monkey fetuses.

Materials and methods

A total of 142 normal gravidas of similar socioeconomic status had a total of 375 serial BPD determinations between 20 and 40 weeks of gestation. The intervals between any two readings ranged from 2 to 6 weeks. Since the fetal ages, at the time of these scans, were well defined (Part I) it was possible to place the BPD readings for each fetus in one of the following three percentile groupings: (1) greater than the seventy-fifth percentile, (2) between the twenty-fifth and seventy-fifth percentiles, and (3) less than the twenty-fifth percentile. Fetuses whose initial BPD values fell exactly on the seventy-fifth percentile level were placed in either of Groups 1 or 2 only after the second BPD reading was obtained. If the second BPD value was greater than the seventy-fifth percentile the fetus was classified in Group 1 (Fig. 1). If the second BPD reading was less than the seventy-fifth percentile

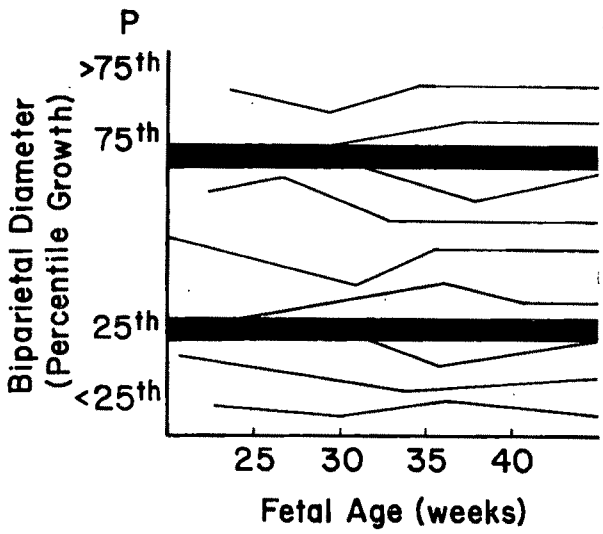


Fig. 1. Fetal BPD growth patterns. Fetal BPD's normally remain in the initially assigned percentile *(P)* rank.

Table I. Probability of changing from one percentile state to P^{th} outcome percentile

Assigned percentile group	*Outcome P^{th}*				
	<25th	*25th*	*50th*	*75th*	*>75th*
>75th	0.00	0.00	0.00	0.02	0.98
50th-75th	0.00	0.00	0.96		0.04
25th-50th	0.07	0.93	0.00		0.00
<25th	0.97	0.03	0.00		0.00

the fetus was classified in Group 2 (Fig. 1). Similarly, fetuses whose first BPD readings fell exactly on the twenty-fifth percentile were classified in either Group 2 or Group 3 depending upon the percentile level of the second BPD value, (Fig. 1). An analysis of the relationship between the observed BPD growth trends and both the gestational age and neonatal birth weights was then carried out.

Results

The results of the study indicate that the BPD's of all the fetuses are separable from as early as 20 weeks of gestation into one of three growth patterns: (1) BPD's greater than the seventy-fifth percentile—50 fetuses fell into this group; (2) BPD's ranging between the twenty-fifth and the seventy-fifth percentiles—62 fetuses fell into this group; (3) BPD's less than the twenty-fifth percentile—30 fetuses fell into this group.

It is also observed that 90 per cent (128 out of 142) of fetuses are normally capable of maintaining their cephalic growth within the initially assigned percentile grouping. The probabilities governing the deviation from any of these percentile limits for this group are shown in Table I.

Eleven of 142 fetuses, however, dropped their initial BPD rank from one percentile level into the next lower rank, as seen in Fig. 2. The extent of the decline and the ultimate neonatal weights are also shown in Fig. 2. The latter BPD changes represent abnormal deviations from the expected normal growth trend. In contrast, three out of 142 fetuses (Fig. 2) increased their BPD percentile level into the next higher rank. All these fetuses did well.

Comment

Two new phenomena not previously reported in human fetal growth are noted in this study. (1) Fetuses carried by normal mothers with a similar socioeconomic status can be clearly separated into those with large, average, and small BPD's. (2) Fetuses assigned an initial cephalic percentile ranking are capable, under normal conditions, of maintaining this level until birth. These two observations are important because they imply a predictable growth pattern for each individual fetus in utero. Such an expected growth potential leads to both a closer assessment of fetal age and to a better evaluation of neonatal weight and outcome. These two parameters will now be discussed separately.

BPD growth pattern vs. fetal age assessment

In order to facilitate the prediction of fetal age from the use of ultrasonic cephalometry, the BPD percentile range corresponding to different weeks of gestation and the percentile range for fetal age equivalent to different BPD measurements (Part I) are shown combined in Table II.

The key to assigning a given fetus a precise gestational age lies in the accurate assessment of the specific fetal head growth pattern, i.e., whether the BPD's of a particular fetus are in the upper, middle, or lower percentile range (Fig. 1). The percentile classification of the head size is possible if two BPD readings are obtained. The first BPD is used to predict the fiftieth percentile fetal age and the second is used to establish a fetal growth trend. The first BPD is best obtained between 20 and 24 weeks of gestation because during this interval of pregnancy the fetal movements are not excessive, leading to a technically reliable measurement; additionally, during this time, the BPD bears a close relationship to fetal age (±10 to 11 days) for fetuses of all sizes.[2] If, for example, the first BPD reading is 5.4 cm., it becomes evident (Fig. 3) that this value can represent one of three fetuses: (1) a 21±-week-old fetus with a large head, (2) a 22±-week-old fetus with an average-sized head, and (3) a 23±-week-

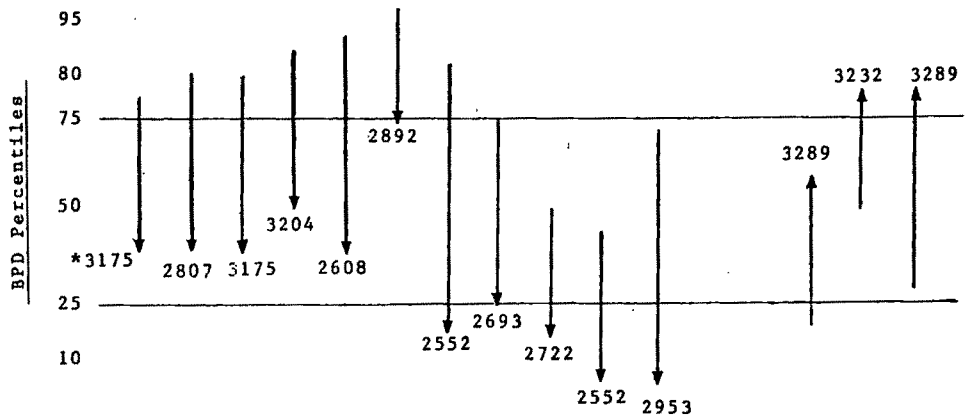


Fig. 2. Abnormal BPD growth trends of 14 fetuses. Fetuses unable to maintain their cephalic percentile rank usually fluctuate only between two percentile groups, i.e. upper to middle, or middle to lower. Last reading in midthird trimester. Asterisk indicates neonatal weight (in grams).

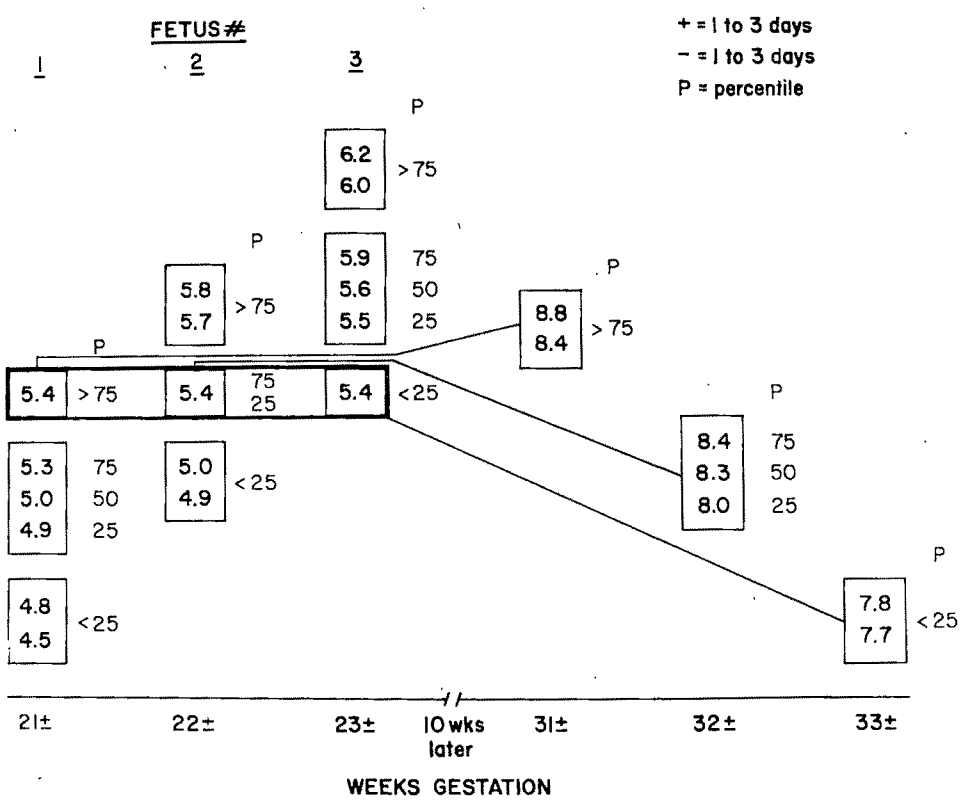


Fig. 3. Fetal growth patterns from BPD of 5.4 cm. The first BPD of 5.4 cm. represents any of three fetuses of differing fetal age (Table II, *B*). A second BPD reading 10 weeks later will identify the fetus as large, average, or small (Table II, *A*) and lead to a closer assessment of fetal age.

old fetus with a small head. It is not possible from this one head measurement of 5.4 cm., to differentiate these three fetal age categories. Therefore, the fiftieth percentile fetal age of 22± weeks (Table II, *B*) is temporarily accepted to estimate the length of pregnancy and carries with it confidence limits of ±10 to 11 days. A second BPD reading 10 weeks later will then identify the head size growth pattern as: large, i.e. above the seventy-fifth percentile, average, i.e., between the twenty-fifth to the seventy-fifth percentile, or small, i.e., below the twenty-fifth percentile. If the BPD 10 weeks later is observed to fall in the average range for 32± weeks the initially assigned fetal age will not have to be changed. If, however, the BPD is shown to

Table II. BPD percentile ranges and measurements for both black and white fetuses

A. BPD percentile values from 16 to 40 weeks

Fetal age (wk.)	BPD percentiles							N
	5	10	25	50	75	80	95	
16	3.1	3.2	3.4	3.7	4.0	4.1	4.5	12
17	3.4	3.5	3.7	4.0	4.3	4.4	4.7	15
18	3.7	3.8	4.0	4.3	4.5	4.6	4.9	22
19	3.9	4.2	4.3	4.5	4.8	4.9	5.1	33
20	4.2	4.5	4.6	4.7	5.0	5.1	5.3	39
21	4.5	4.8	4.9	5.0	5.3	5.4	5.5	40
22	4.9	5.0	5.2	5.3	5.6	5.7	5.8	48
23	5.2	5.3	5.5	5.6	5.9	6.0	6.2	57
24	5.5	5.6	5.8	5.9	6.2	6.3	6.6	50
25	5.8	5.9	6.0	6.2	6.5	6.6	7.0	47
26	6.1	6.2	6.3	6.6	6.8	6.9	7.3	43
27	6.4	6.5	6.7	6.9	7.1	7.2	7.6	51
28	6.6	6.7	7.0	7.2	7.4	7.5	7.9	51
29	6.8	6.9	7.3	7.5	7.8	7.9	8.3	53
30	7.1	7.2	7.6	7.8	8.0	8.2	8.6	50
31	7.3	7.4	7.8	8.0	8.2	8.4	8.8	48
32	7.5	7.6	8.0	8.3	8.4	8.6	9.0	47
33	7.7	7.8	8.3	8.5	8.6	8.8	9.1	50
34	7.9	8.0	8.5	8.7	8.9	9.1	9.3	50
35	8.2	8.3	8.7	8.8	9.1	9.3	9.6	49
36	8.3	8.5	8.9	9.0	9.3	9.4	9.7	48
37	8.4	8.8	9.0	9.2	9.4	9.5	9.8	43
38	8.5	8.9	9.1	9.3	9.5	9.6	9.9	42
39	8.7	9.0	9.2	9.4	9.6	9.7	10.0	29
40	8.9	9.3	9.4	9.5	9.7	9.8	10.1	15

be higher or lower than the percentile range for 32± weeks the earlier accepted fiftieth percentile fetal age estimate will have to be decreased or increased, respectively. As an illustration, if the initial BPD of 5.4 cm. represents the average cephalic size of a fetus 22± weeks of age (Fig. 3), it is normally expected 10 weeks later to remain in the same average (twenty-fifth to seventy-fifth percentile) range for 32± weeks, i.e., fall between 8.0 and 8.4 cm. (Table II, *A* and Fig. 3). If in fact the second reading falls in this range then the initially assigned fetal age of 22± weeks will not have to be changed. Its accuracy, however, is greatly enhanced because the specific growth pattern of this fetus is now known. The confidence limits for 22 weeks will then be reduced from the previously reported ±10 or 11 days to ±1 to 3 days.

In the event that the initial BPD of 5.4 cm. represents the cephalic size of a large fetus, i.e. above the seventy-fifth percentile range for 21± weeks of age (Fig. 3), it is expected 10 weeks later to remain in the same high range (above the seventy-fifth percentile) for 31± weeks. The eightieth and ninety-fifth BPD percentile values for 31± weeks are 8.4 to 8.8 cm. (Table II, *A* and Fig. 3). If in fact the second reading falls in this range the initially assigned fetal age of 22± weeks will have to be corrected to 21± weeks. The

Table II.—Cont'd

B. Fetal age percentile values for BPD's from 3.5 to 9.5 cm.

BPD	Fetal age percentiles (wk)*						
	5	10	25	50	75	80	95
3.5	17+	17	16+	16	16−	16−	15+
3.6	18	17+	17	16+	16	16	15+
3.7	19	18	18	17−	16	16	16
3.8	19	18+	18+	17	16+	16+	16
3.9	19+	19	18+	17+	17−	17−	16
4.0	19+	19	19−	18−	17	17−	16
4.1	19+	19	19−	18	17+	17+	16
4.2	20−	19+	19	18+	17+	17+	16+
4.3	20	20−	19+	19−	18−	18−	17−
4.4	20+	20	20−	19	18+	18	17
4.5	21−	20+	20	19+	19−	18	17+
4.6	21	21−	20+	20−	19	18+	18−
4.7	21+	21	21−	20	19+	19	18
4.8	21+	21	21	20+	20−	19+	18+
4.9	22−	21+	21+	21−	20	19+	19−
5.0	22	22	22−	21	20+	20−	19
5.1	22+	22	22−	21+	20+	20	19+
5.2	23−	22+	22	22−	21−	20+	20−
5.3	23	23−	22+	22−	21	21−	20
5.4	24−	23+	23−	22	21+	21+	20+
5.5	24	24−	23	22+	22−	21+	21−
5.6	24	24−	23+	23−	22	22−	21
5.7	24+	24	24−	23	22+	22+	21+
5.8	25−	24+	24	23+	23−	23−	21+
5.9	25	25−	24+	24−	23	23−	22−
6.0	25+	25	25−	24	23	23	22−
6.1	26−	25+	25	24+	23+	23+	22
6.2	26	26−	25+	25−	24−	23+	22+
6.3	26+	26	26−	25	24	24	23−
6.4	27−	26+	26	25+	24+	24+	23+
6.5	27+	27	26+	26−	25	25	24−
6.6	28−	27+	27−	26	25+	25+	24−
6.7	28	28−	27	26+	26−	26−	24
6.8	28+	28	27+	27−	26	26−	24+
6.9	29	28+	28−	27	26+	26+	25−
7.0	29+	29−	28	27+	27−	26+	25−
7.1	30	30−	28+	28−	27	27−	25+
7.2	31−	30−	29−	28−	27+	27	25+
7.3	31	30	29	28	28−	27+	26−
7.4	32−	31	29+	28+	28−	27+	26
7.5	32	32−	30−	29−	28+	28−	26+
7.6	33−	32	30	29	28+	28	27−
7.7	33	32	30+	30−	29−	28+	27
7.8	33	32+	31−	30	29−	29−	27+
7.9	33+	33	31+	30+	29	29	28−
8.0	34	33+	32	31−	29+	29+	28
8.1	34+	34	32+	31	30−	30−	28+
8.2	35	35−	33−	31+	30	30	29−
8.3	36−	35	33	32	31	30+	29
8.4	36	36−	33+	32+	31	31−	29
8.5	36+	36−	34−	33	31+	31	29+
8.6	36+	36−	34	33+	31+	31	29+
8.7	37−	36	35−	34	32−	31−	30−
8.8	37	36+	35+	34+	32	32−	30
8.9	38−	37	36	35+	33	32+	31
9.0	38+	37+	37−	36−	33+	33	32−
9.1	39−	38	37	36+	34	34	32+
9.2	39	39−	37+	36+	35	35	33
9.3	39+	39−	38−	37−	35	35	34−
9.4	40−	39	38	37	36−	35	34+
9.5	40	39+	38+	37+	36	35	35−

*+ = 1 to 3 days; − = 1 to 3 days.

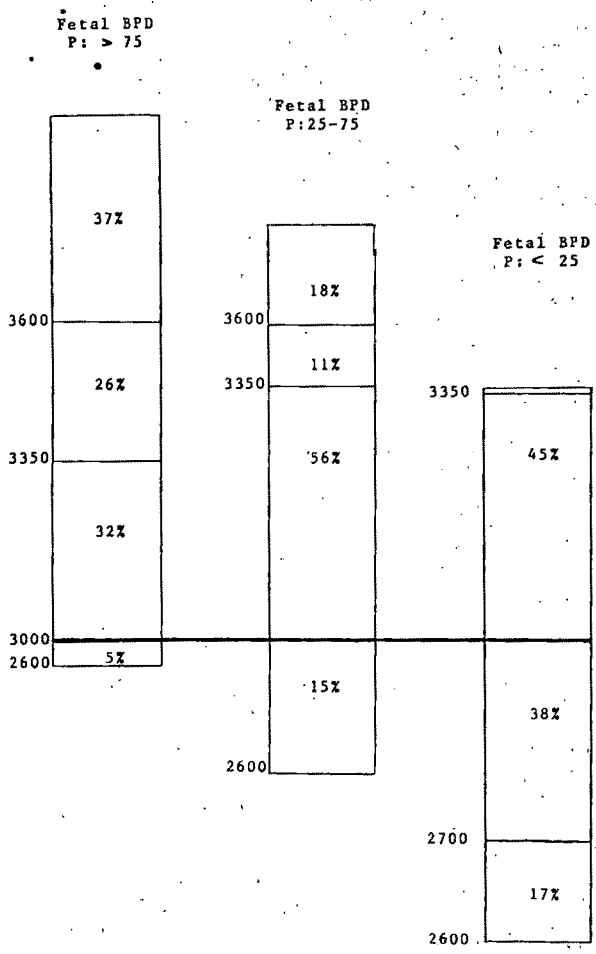


Fig. 4. Percentage distribution of neonatal weights (in grams) according to fetal BPD growth patterns. Of the fetuses with BPD's above the seventy-fifth percentile, 95 per cent weigh over 3,000 grams; 85 per cent of fetuses with average BPD's (twenty-fifth to seventy-fifth percentile) weigh over 3,000 grams; 55 per cent of fetuses with small BPD's (below the twenty-fifth percentile) weigh under 3,000 grams.

confidence limits for this fetal age are, however, reduced to ±1 to 3 days instead of ±10 to 11 days. Similarly, a small fetus (below the twenty-fifth percentile) with an initial BPD reading of 5.4 cm. (fetal age 23± weeks) (Fig. 3) is expected to stay below the twenty-fifth percentile 10 weeks later at age 33± weeks. Therefore, if the second reading falls below the twenty-fifth percentile for 33± weeks (Table II, *A* and Fig. 3), then the earlier fetal age of 22± weeks will have to be corrected to 23 weeks ±1 to 3 days.

Regarding the fetus unable to maintain its cephalic percentile rank because of an unfavorable intrauterine environment, it is noted (Fig. 2) that the BPD will usually fluctuate only between two percentile ranks. As a result, the predicted fetal age in such a case will range between the mean and either extreme end, which is a deviation of 10 or 11 days rather than ±10 to 11 days.

Table III. Percentiles of birth weight from 198 normal term pregnancies

Percentiles	*Corresponding birth weight*	*Grams*
5	5 lb. 12 oz.	2,608
10	6 lb. 0 oz.	2,694
20	6 lb. 7 oz.	2,892
25	6 lb. 9 oz.	2,948
50	7 lb. 3 oz.	3,232
75	7 lb. 14 oz.	3,544
80	8 lb. 0 oz.	3,601
95	9 lb. 10 oz.	4,338

In conclusion, it is therefore noted that by employing serial cephalometry and separating fetuses into three percentile growth patterns, it becomes possible to predict fetal age from the sonar BPD with greater precision.

BPD growth potential vs. neonatal weight and outcome

Neonatologists are beginning to look at the fetus who fails to thrive in utero in two ways. The first is by comparing its birth weight with a statistically defined standard (the third* to the tenth percentile) for a given gestational age; fetuses who fall within such a percentile range are referred to as small-for-gestational-age (SGA) or intrauterine growth–retarded (IUGR) fetuses. The second is by looking for the presence of soft tissue wasting or fetal malnourishment (FM). A malnourished fetus is one whose birth weight may be above the third to the tenth percentile for its age, yet it clearly shows evidence of loss of subcutaneous tissue and a decrease in the muscle mass over the arms, thighs, and buttocks. FM, representing wasting, is a more severe and acute form of malnutrition that can affect both normal and IUGR fetuses. When it does it is associated with an increased incidence of intrauterine fetal death and perinatal asphyxia.[3] If one, therefore, knows the intrauterine potential of each fetus from the sonar BPD, deviations from the expected norm for a given fetus will become more readily apparent and more meaningful in delineating the development of abnormalities. The BPD of a particular fetus is no longer compared to a normal mean value, but rather to the expected potential for that fetus in question. For example, this study shows that 95 per cent of fetuses whose sonar BPD readings consistently fall in the upper percentile range, i.e. above the seventy-fifth percentile, have a birth weight in excess of 3,000 grams—with two-third of these fetuses weighing over

*In this paper the third percentile is used to define IUGR.

the fiftieth birth weight percentile (BWP) (Fig. 4 and Table III). The remaining 5 per cent of fetuses who maintain their cephalic ranking, possibly because of a less favorable intrauterine environment, weigh below 3,000 grams (Fig. 4). In this study none of the latter group was labeled as an IUGR or FM neonate, although it is theoretically possible that some may develop IUGR. The inference then is as follows: The majority of fetuses who maintain their BPD ranking above the seventy-fifth percentile level weigh over 3,000 grams, but those who weigh below that level, although small, are still considered normal by present pediatric standards. In contrast, seven fetuses whose initial BPD ranking was above the seventy-fifth percentile showed a decrease of the BPD value to the next lower level (Fig. 2). All of these fetuses weighed below the fiftieth BWP and two weighed less than the twentieth BWP. This observation suggests, at present, that fetuses who drop their BPD ranking as compared to those who maintain their initial percentile level are more likely to be small neonates, and border on IUGR or FM.

Analysis of the data in this report also shows that two-thirds of the fetuses whose serial sonar BPD values fall in the midpercentile range (twenty-fifth to seventy-fifth) have birth weights in the average range of 3,000 to 3,544 grams (twenty-fifth to seventy-fifth BWP) (Fig. 4). The remaining one-third of these fetuses, however, are equally divided into two categories: the first, probably deriving maximum benefit from their uterine environment, weigh more than the seventy-fifth BWP; the second, not being as fortunate, weigh less than the twenty-fifth BWP. Nevertheless, in this study none of the latter fetuses has been classified as an IUGR or FM neonate. In contrast, four fetuses who started with average BPD's dropped this ranking in time to below the twenty-fifth percentile level (Fig. 2). All of these fetuses weighed below 3,000 grams or below the twenty-fifth BWP, and three fell below the tenth BWP. It is then again suggestive that a fall from the expected BPD growth pattern is more likely to lead to small neonates, some of whom maybe, frankly, growth retarded.

The third group of fetuses described in this paper have small heads consistently falling below the twenty-fifth BPD percentile level. It is observed (Fig. 4) that they all weigh below the fiftieth BWP (Fig. 4 and Table III); furthermore, 55 per cent of them weigh under 3,000 grams (Fig. 4). This latter group possibly represent the lower part of the normal distribution curve of fetal growth. As such, however, they are highly susceptible to adverse changes in their uterine milieu and require close perinatal monitoring. In fact, one-third of this group did weigh between the fifth and the tenth BWP.

In summary, the data from this study suggest that it is now possible to objectively evaluate the individual growth potential for each fetus, in utero, in a meaningful prospective manner.

REFERENCES

1. Sabbagha, R. E., Turner, J. H., and Chez, R. A.: Sonar biparietal diameter growth standards in the rhesus monkey, Am. J. Obstet. Gynecol. **121:** 371, 1975.
2. Sabbagha, R. E., Turner, J. H., Rockett, H., et al.: Sonar BPD and fetal age. Definition of the relationship, Obstet. Gynecol. **43:** 7, 1974.
3. Scott, K. E., and Usher, R. H.: Fetal malnutrition: Its incidence, causes and effects, Am. J. Obstet. Gynecol. **94:** 951, 1966.

Current practices in antepartum and intrapartum fetal monitoring

P. V. DILTS, JR., M.D.

Memphis, Tennessee

Survey forms were sent to 360 Ob./Gyn. residency programs in the United States and Canada with responses from 279 concerning usage of various types of fetal monitoring. The results are presented and discussed.

THE VALUE of electronic fetal monitoring has been well demonstrated.[1-3] Only one report has appeared to the contrary.[4] However, when the statement was made at the Society for Obstetrical Anesthesia and Perinatology (Philadelphia, April 4 and 5, 1975) that all anesthesia residents are taught electronic fetal monitoring, no answer concerning residencies in obstetrics and gynecology was available. Accordingly, a survey of obstetrics and gynecology residencies in the United States and Canada was made. The questionnaire covered other types of ante- and intrapartum monitoring, since these data were also unavailable. The intent of the survey is several-fold: (1) to accumulate a data base of present practices, (2) to allow residency directors comparison with other areas and national norms, (3) to begin formulation of national standards available to the various Review Committees, and (4) to allow nonteaching hospitals to anticipate the needs of future practitioners of obstetrics and gynecology.

Methods

A questionnaire was sent to the directors of all residency programs in obstetrics and gynecology (360) in the United States and Canada in April, 1975. A follow-up mailing was sent to all nonresponding programs in June, 1975. In addition, the questionnaire was included in the *Society for Obstetrical Anesthesia and Perinatology Newsletter* in early June, 1975.

From the Department of Obstetrics and Gynecology, The University of Tennessee College of Medicine.

Received for publication January 23, 1976.

Revised May 4, 1976.

Accepted May 21, 1976.

Reprint requests: Dr. P. V. Dilts, Jr., Department of Obstetrics and Gynecology, The University of Tennessee College of Medicine, 809 Madison Ave., Memphis, Tennessee 38163.

Results

Responses were received from 279 programs, 263 in the United States and 16 in Canada. Results are tabulated for the entire group (Table I) and for two types of subdivisions: (1) Programs from Canada, and, in the United States, Military, University, University-affiliated, and nonaffiliated programs; and (2) programs with fewer than 2,000, 2,000 to 5,000, or more than 5,000 deliveries annually (Table II). University programs are defined in this survey as those with the title "University." Affiliated programs are those listed as such in the *Directory of Approved Residences* (American Medical Association) or in which the author knows of an affiliation. Unaffiliated programs are all others except military or Canadian.

The number of residents in each year of a program was compared to the number of patients undergoing electronic fetal monitoring to determine if the resident's educational needs or work performance might influence the availability of monitoring by contingency table analysis (Fisher's Exact Test or R × C chi-square analysis). The University programs with fewer than 2,000 deliveries showed positive correlation between number of residents and number of patients monitored ($p < 0.004$, as did the total group of programs ($p < 0.00001$), the entire group of University programs ($p < 0.00001$), and the unaffiliated programs ($p < 0.0005$). The number of deliveries for the total group was positively correlated with the number of patients monitored at fewer than 2,000 ($p < 0.049$) and at more than 5,000 ($p < 0.04$).

The same analyses were used to compare the per cent of patients who were "private" with the per cent of patients monitored. Positive correlation was found in University programs with 2,000 to 5,000 deliveries ($p < 0.0005$), in affiliated programs with fewer than 2,000 deliveries ($p < 0.02$), in the total group of affiliated programs ($p < 0.046$), and in the total group

Table I. Responses for total group

	Amniotic fluid										
	L/S ratio	*Creatinine*	*Alpha feto-protein*	*Bilirubin*	*Amnioscopy*	*Amniography*	*Genetic analysis*	*HPL*	*Alkaline phosphatase*	*Estriol/ estrogen*	*Ultra-sound*
Yes	277 (99.3)*	271 (97.1)	169 (60.8)	271 (97.1)	108 (38.8)	220 (79.4)	253 (90.7)	150 (54.3)	184 (66.4)	277 (99.3)	255 (91.4)
Total	279	279	278	279	278	277	279	276	277	279	279

*Numbers in parentheses are per cent yes.

Table II. Responses by size and location—yes/no

	Amniotic fluid									
Type of program, annual deliveries	*L/S ratio*	*Creatinine*	*Alpha feto-protein*	*Bilirubin*	*Amnio-scopy*	*Amnio-graphy*	*Genetic analysis*	*HPL*	*Alkaline phosphatase*	*Estriol/ estrogen*
University:										
<2,000	26/0	25/1	18/8	25/1	11/15	22/4	24/2	12/14	17/9	25/1
2,000-5,000	50/0	50/0	33/17	50/0	22/28	43/7	48/2	30/20	30/20	50/0
>5,000	21/0	19/2	13/8	21/0	9/12	21/0	21/0	13/8	13/8	21/0
Affiliated:										
<2,000	33/0	33/0	20/13	33/0	16/17	20/13	29/4	20/12	21/11	33/0
2,000-5,000	32/0	31/1	15/16	30/2	10/22	24/7	30/2	14/17	19/12	31/1
>5,000	2/0	2/0	2/0	2/0	1/1	2/0	2/0	2/0	2/0	2/0
Unaffiliated:										
<2,000	40/0	37/3	18/22	37/3	15/25	28/12	32/8	18/22	29/11	40/0
2,000-5,000	40/2	42/0	26/16	41/1	5/36	29/12	36/6	24/17	31/11	42/0
>5,000	4/0	4/0	2/2	3/1	1/3	4/0	3/1	1/3	1/3	4/0
Military:										
<2,000	9/0	9/0	5/4	9/0	5/4	9/0	8/1	4/5	6/3	9/0
2,000-5,000	4/0	3/1	2/2	4/0	2/2	4/0	4/0	2/2	3/1	4/0
Canada:										
<2,000	2/0	2/0	1/1	2/0	0/2	2/0	2/0	2/0	2/0	2/0
2,000-5,000	8/0	8/0	8/0	8/0	5/3	6/2	8/0	3/5	5/3	8/0
>5,000	6/0	6/0	6/0	6/0	6/0	6/0	6/0	5/1	5/1	6/0

Table III. Comparison of number of monitors to number of deliveries

	Type														
	University			*Affiliated*			*Unaffiliated*			*Military*		*Canada*		
	<2,000	*2,000-5,000*	*>5,000*	*<2,000*	*2,000-5,000*	*>5,000*	*<2,000*	*2,000-5,000*	*>5,000*	*<2,000*	*2,000-5,000*	*<2,000*	*2,000-5,000*	*>5,000*
Number*	25	50	20	32	31	2	39	40	3	9	4	2	8	4
Mean†	254	321	361	268	351	301	326	351	582	249	349	90	163	209
S.D.	±132	230	176	121	230	72	139	208	382	77	96	—	85	55

*Number of programs reporting.
†Patients per machine.

of programs with 2,000 to 5,000 deliveries ($p < 0.05$).

Table III presents data concerning the number of patients monitored by each machine in use for the various types and size of programs.

Comment

The purpose of the survey is straightforward: to find out current practices. The survey form was not perfect. Some of the antepartum tests presently in use were inadvertently left out. Perhaps this reflects the bias of the author. Some programs may have confused the Po_2 and Pco_2 scalp sample questions with neonatal cord blood studies. The total response of 279 out of 360 is excellent.

Table I is self-explanatory and indicates that most programs use the L/S ratio (similar tests included),

Fetal monitor	Oxytocin challenge test	Scalp		
		pH	P_{O_2}	P_{CO_2}
278 (99.6)	269 (96.8)	184 (67.6)	136 (52.1)	146 (55.9)
279	278	272	261	261

Ultrasound	Fetal monitor	Oxytocin challenge test	Scalp			Total responding
			pH	P_{O_2}	P_{CO_2}	
25/1	26/0	26/0	19/6	15/9	14/10	26
47/3	50/0	48/2	38/11	31/15	33/14	50
21/0	21/0	21/0	19/2	3/16	13/6	21
32/1	33/0	31/2	22/11	17/12	17/11	33
29/3	32/0	31/1	22/10	20/11	20/12	32
2/0	2/0	2/0	2/0	2/0	2/0	2
34/6	39/1	37/3	20/16	15/25	15/25	40
34/8	42/0	41/1	17/24	12/26	11/26	42
3/1	4/0	4/0	1/3	1/3	1/3	4
9/0	9/0	9/0	7/2	6/3	6/3	9
4/0	4/0	4/0	3/1	2/2	2/2	4
2/0	2/0	2/0	1/1	1/1	1/1	2
7/1	8/0	8/0	7/1	5/2	5/2	8
6/0	6/0	5/0	6/0	6/0	6/0	6

amniotic creatinine and bilirubin, and amniography. Genetic analysis, estriol or total estrogen, ultrasound, fetal monitoring, and the oxytocin challenge test are similarly popular. Amnioscopy is not used by most programs. Scalp sampling is used by most, as is human placental lactogen(HPL), but with much less popularity. Alpha fetoprotein is new enough that conclusions may be questioned.

Table II presents the same data divided by size and type of program. The types may be fuzzy, since the "Directory" is not completely clear. The author had to guess in several instances between affiliated and unaffiliated. However, the numbers are great enough that this should not be a major cause of error. It is unavoidable.

The comparison (Table III) of number of patients monitored by each machine for the various types and size of program may be used by hospitals and directors as a guide to the number of machines needed at a given institution. The large standard deviations are a reflection of wide variation in practice. Second, the difference may represent inaccurate reporting, since the number monitored had to be calculated from the total number of deliveries and the estimate of per cent monitored. Third, more accurate record keeping is necessary at all levels. Unaffiliated programs appear to have the smallest number of monitors available, which may indicate an even lower monitor rate than reported, since efficiency is unlikely to differ markedly.

Chi-square analysis indicates that the more residents a program has, the more patients are likely to have electronic fetal monitoring. Hopefully, this does not carry over to hospitals without residency programs; however, no data are available. Similarly, hospitals with fewer than 2,000 or more than 5,000 deliveries annually had a higher rate of monitoring. The broad group with 2,000 to 5,000 deliveries correlates less well. Private patients also were monitored more frequently.

These data and this survey are a reasonably accurate statement of current practices in hospitals with residency programs in obstetrics and gynecology. Each director may compare his own program with those of like institutions. Hospitals without programs may make similar use of the survey. Finally, the various review committees may make use of these data in establishing standards.

Fetal or pregnancy monitoring of all types has added greatly to our understanding of pregnancy. The current literature indicates that combination of the various types of monitoring can and does increase perinatal survival and well being. Just as important is the urgency with which we must be certain that all physicians, nurses, and hospitals providing maternity care can and do offer these services to their patients. The record in our "teaching" hospitals is good but *not good enough.* No data are available for nonteaching hospitals.

Table II indicates that the Canadian and military programs have the greatest number of "0's" in the "No" column. Perhaps this reflects "governmental" medicine. It definitely reflects greater availability of these types of monitoring. All of our residency programs must offer and teach the use of all of the accepted types of monitoring.

The Residency Review Committee, The American Board of Obstetrics and Gynecology, and other responsible accrediting agencies must begin to assess these questions in their review processes. The American College of Obstetricians and Gynecologists must issue Bulletins, Policy Statements, and The Manual of Standards covering use of all types of monitoring. Obviously, many other similar methodologies should also be assessed in perinatology and in the rest of obstetrics and gynecology.

REFERENCES

1. Paul, R. H., and Hon, E. H.: Clinical fetal monitoring. V. Effect on perinatal outcome, AM. J. OBSTET. GYNECOL. **118:** 529, 1974.
2. Quilligan, E. J., and Paul, R. H.: Fetal monitoring: Is it worth it? Obstet. Gynecol. **45:** 96, 1975.
3. Hon, E. H., Zannini, D., and Quilligan, E. J.: The neonatal value of fetal monitoring, AM. J. OBSTET. GYNECOL. **122:** 508, 1975.
4. Haverkamp, A. D., Thompson, H. E., McFee, J. G., and Cetrulo, C.: The evaluation of continuous fetal heart rate monitoring in high risk pregnancy, AM. J. OBSTET. GYNECOL. **125:** 310, 1976.

Microcirculation of the rat placenta

Scanning and transmission electron microscopic observations on fetal blood vessels

MARY M. L. LEE
EDWARD W. DEMPSEY†
New York, New York

The fetal circulation of normal rat placenta was studied by parallel examination with the scanning electron microscope (SEM) and the transmission electron microscope (TEM). By examining casts of vessels injected with latex and prepared by corrosion in hypochlorite solutions, the fetal arteries, veins, and capillaries of the placenta could be traced in the scanning electron microscope and, in addition, the ultrastructural details of microcirculation and luminal surfaces could be studied. Cast specimens showed fetal arteries entering the center of the placenta and branching into long, thin vessels which traversed almost the entire thickness of the placenta before dividing into a markedly tortuous capillary network. The smooth-surfaced capillary vessels located at the arteriolar end flowed into a much less tortuous prevenous capillary network which conducted the blood into collecting venules and veins. Placental blood vessels examined by the TEM provided evidence that details observed by the SEM were accurate for the ultrastructural appearance of fetal arteries, capillaries, and veins.

INTRAVASCULAR casts have been studied by scanning electron microscopy in such organs as kidney,[1, 2] and lungs.[3] To date, however, we are not aware of any such studies on the microcirculation of the placenta. We are, therefore, presenting some observations on the normal placental circulation in rats and suggesting that this microcirculation may be visualized in ultrastructural detail when corrosion preparations of latex casts are examined in scanning electron microscopy. Moreover, the great depth of field together with the high resolving power of the scanning electron microscope allow perception of three-dimensional relationships of the microcirculatory vessels and of their luminal surfaces.

Corrosion-cast specimens have previously been made by Bøe[4] on rat placenta, by Arts[5] on human placenta, and more recently by Arts and Lohman[6] on rhesus monkey placenta. While these vascular studies have contributed to our knowledge of placental circulation, none of the cast specimens was examined for ultrastructural details. Visualization of the microcirculation, especially at the capillary level, would require microscopic examination. Scanning electron microscopic examination of placental tissue has been concentrated mainly on topography[7] and has only recently been employed for examination of the blood vessels of the human placenta.[8] The present investigation correlates the results of the two types of microscopic examinations. We have described the ultrastructural appearances of fetal blood vessels from normal rat placenta as observed in thin sections in the transmission electron microscope and in latex casts examined in the scanning electron microscope. These observations are preliminary to description of changes in the microcirculation of the placenta when affected by pathologic lesions resulting from aging, drugs, or maternal disease.

From the Department of Anatomy, Columbia University College of Physicians and Surgeons.

This study was supported by National Institutes of Health Grants GM-15289 and GM-00257.

Received for publication January 15, 1976.

Revised April 2, 1976.

Accepted May 10, 1976.

Reprint requests: Dr. Mary M. L. Lee, Department of Anatomy, Columbia University College of Physicians and Surgeons, 630 W. 168th. St., New York, New York 10032.

†*Died on January 9, 1975.*

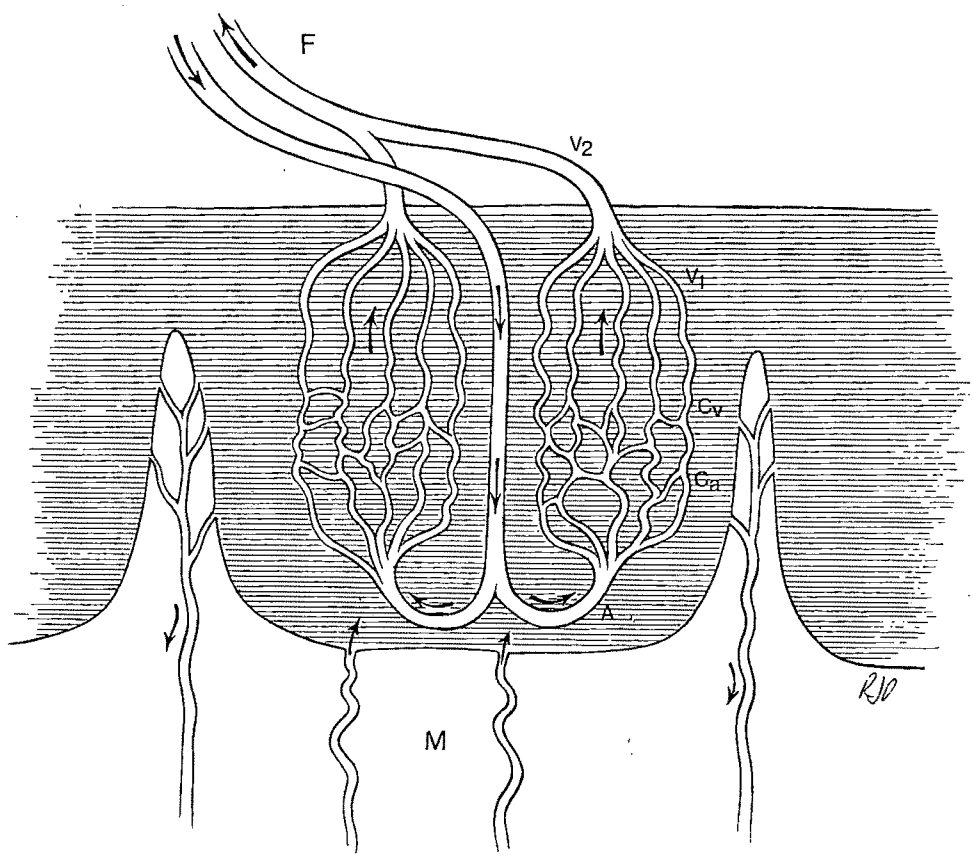


Fig. 1. Diagram of the fetal circulation *(F)* in rat placenta. Thin, straight arteries *(A)* at the fetal side traverse almost the entire thickness of the placenta before branching at the maternal side into a dense, tortuous mass of capillaries *(C_a)*. This capillary network then forms anastomoses with a less tortuous, prevenous capillary network *(C_r)*. The blood is then conducted into a series of wide-lumen venules *(V_1)* which flow into large-size veins *(V_2)* to be returned to the hilus and umbilical cord. The maternal arterial blood of the rat placenta enters through a large central artery which then divides, forming numerous branches *(M)* which spread out laterally to supply the organ. The maternal blood flow is in the opposite direction to that of fetal arterial blood. This forms a counter-current flow which provides for efficient exchange of materials between mother and fetus.

Materials and methods

Ten female rats (18 to 20 days pregnant) of the Sprague-Dawley strain weighing approximately 200 grams each were used for this experiment. All animals were fed a diet of regular chow (Purina) and tap water. After the animal was anesthetized with sodium pentobarbital administered intraperitoneally (30 mg. per kilogram), a V-shaped incision was made in the lower abdomen to expose the uterine horns. The uterine muscle layers, amnion, and yolk-sac of one side were cut with an extra-fine dissecting scalpel to expose the fetuses and placentas. The uterine horn of one side with three to four fetuses was used for TEM; the other uterine horn was used for the injection corrosion-cast technique. To obtain placental tissue for TEM, the umbilical cord was ligated and cut distally; one placenta was removed at a time from the uterine wall. Initially, the placenta was divided at the mid-zone, with further subdivisions of the tissues made in a drop of Dalton's fixative. The tissue was fixed in the cold at 4° C. in Dalton's chrome-osmium solution for 2 hours. Then the tissue was dehydrated through alcohol series and embedded in Swiss Araldite (Durcupan). The tissue blocks were sectioned on a Porter-Blum MT-1 microtome and stained with lead citrate. The sections were examined in a RCA 3-G electron microscope.

To prepare casts for the scanning electron microscope, the remaining uterine horn was cut to expose the fetuses for in situ placental injections. First a small cotton swab was placed beneath the gelatinous umbilical cord, then the umbilical artery or vein was cut to facilitate injection of a latex mixture (Cementex*) into

*Cementex Corporation, Inc., New York, New York.

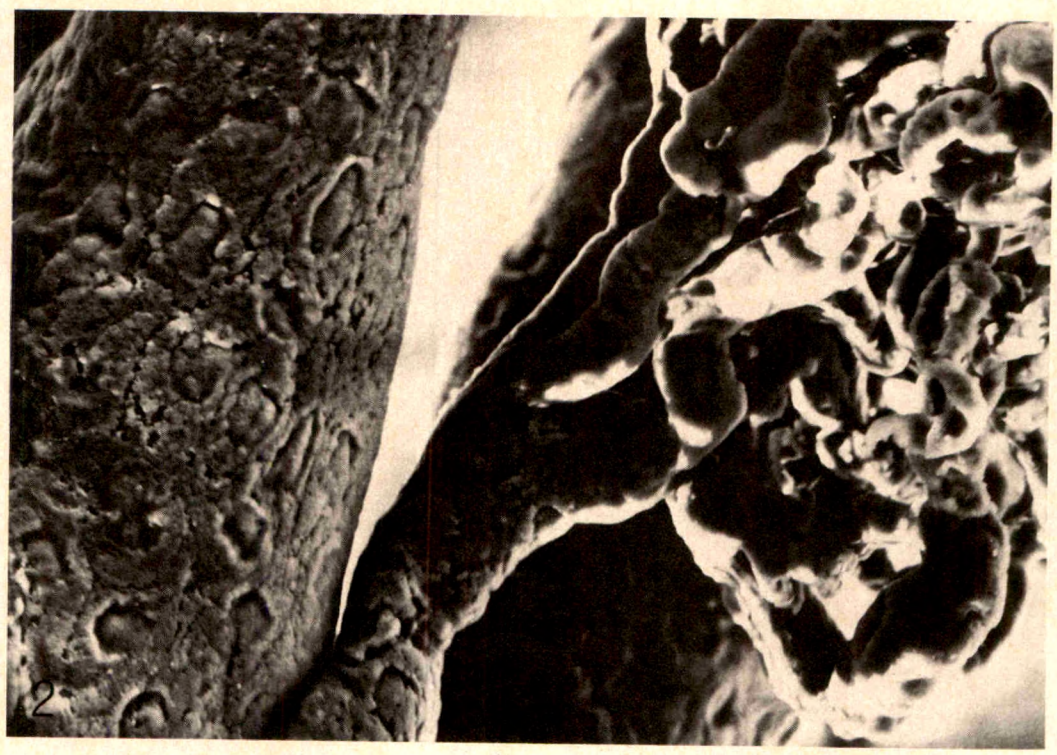


Fig. 2. Scanning electron micrograph of a latex cast from placenta of rat. The stem vessel (fetal artery) has a small subdivision branch located on the right. The surface of the arterial vessel shows imprints of nuclear impressions made by bulging nuclei of endothelial cells lining the luminal surface. The small side-arm branch subdivides to form a capillary network (×240.)

the umbilical artery or vein by a 25 gauge needle attached to a 2 c.c. syringe. For a single-injection specimen, about 0.5 c.c. of 60 per cent Cementex (diluted with distilled water) was injected into the blood vessels at a slow rate; about 3 minutes were required for the 0.5 c.c. injection. For double-injection studies, yellow Cementex was introduced into the artery and blue Cementex into the vein. In these cases the umbilical vessels were not severed and injections were made first into the artery and then into the vein. When all of the placentas had been injected, the animal was left at room temperature for 3 hours to permit the Cementex to solidify; then each umbilical cord was cut and the placenta was removed from the uterus. The specimens were fixed in 10 per cent formalin for a month to allow for further hardening of the latex. The double-injection specimens were sliced in sagittal sections to be studied for the pattern of distribution of arterial and venous vessels in the rat placenta. The single-injection placentas were macerated by treatment in a solution of sodium hypochlorite (Clorox) for 2 to 3 days with daily changes. Following this treatment, the resulting latex casts of the blood vessels were washed gently in several rinses of distilled water, air dried, and then carefully teased apart with a jeweler's forceps into small groups of vessels for detailed viewing. The remaining steps were similar to those used in preparing renal glomerular cast specimens.[1] Upon completion of the preparations, the resulting placental vascular casts were viewed and photographed on a Cambridge Stereoscan Mark II SEM.

Observations

By microscopic examination of the double-injection specimens, we were able to establish the general pattern of fetal arterial and venous circulation in the rat placenta. A simplified drawing representing the fetal circulation in the rat placenta is shown in Fig. 1. The arteries branch after entering the placenta and send thin, straight vessels *(A)* which traverse almost the entire thickness of the placenta before branching at the maternal side into a thick mass of capillaries *(C_a)* which is markedly tortuous in appearance. This capillary network then anastomoses with a less tortuous capillary network *(C_v)*. The vessels here are slightly wavy but have an essentially straight course. From this capillary network, the blood is conducted through a series of wide-lumen venules *(V_1)* and then into large veins *(V_2)* to be returned to the umbilical cord. The SEM provided the appearance of the vasculature, and

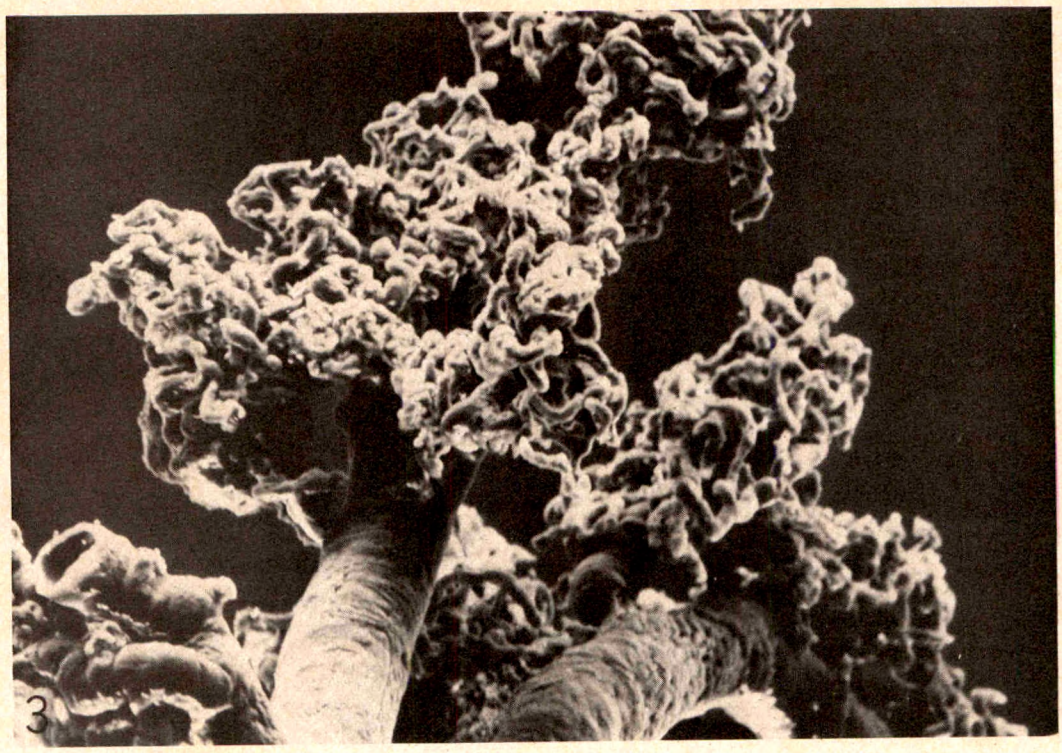


Fig. 3. Placental cast showing two arteries (center) traveling toward the maternal side of the organ and terminating in a rich capillary network there. The small caliber capillaries exhibit a twisting, winding appearance. (×135.)

the course of blood flow was reconstructed from SEM observations as well as from double-injection specimens. The maternal arterial blood enters the placenta through a large centrally located artery which divides into numerous branches *(M)* to supply the organ. The maternal blood flows in opposite direction to that of the fetal arterial blood. To obtain a detailed picture of the microcirculation, it was necessary to examine the single injection cast specimens in the SEM.

Scanning electron microscopy. Casts prepared from the rat placenta were examined with the SEM. A difference was observed between the arterioles and the capillaries which was not noted in previous placental injection studies for the arterial vessels in our latex casts have a rough surface contour with indentations presumably representing the bulging nuclei of endothelial cells lining the vessels (Fig. 2). Similar observations on arterioles have been made in renal glomerular latex cast studies.[1, 2] The capillaries, in contrast, have a relatively smooth surface contour and a densely packed, tortous appearance (Figs. 3 and 5). The arterioles supplying this profuse capillary network originate from arteries which enter near the center of the placenta; these branch, sending thin, straight vessels directly across the thickness of the placenta (Fig. 4) where, on the maternal side of the organ, the arterioles branch laterally to form a profuse network of capillaries. It is interesting to note that the long, straight conducting vessels may have side-arm branches of a very small caliber which can suddenly ramify from the main vessel. Such a side-arm branch, coming off at right angles, is shown in Fig. 4. Another delicate branch which has just furcated from the stem vessel is shown in Fig. 2. The abrupt change in blood vessel size may be of significance in the hemodynamics of the fetal arteriolar circulation (see below for additional comments).

While the capillary network on the arteriolar side may be characterized as dense and tortuous, the capillary network on the venous side is characterized by straighter vessels, all radiating toward the larger diameter venules (Figs. 6 and 7). It is of interest that the capillaries, whether at venous or arteriolar areas, are of fairly uniform diameter with no marked dilatations or constrictions to alter the blood flow.

Transmission electron microscopy. The fetal capillaries provide an excellent study of endothelial cells and pericytes. The capillary lumen varies slightly in diameter and may have two or three endothelial cells forming the lining. These cells contain a few



Fig. 4. Placental cast of fetal arteries shows two long, straight vessels which branch into a thick, tortuous capillary network at the maternal side (top). The arrow (right) points to a small side-arm branch of the fetal artery which demonstrates an abrupt change in blood vessel size from the wide-diameter artery to the small-caliber off-shoot. This abrupt transition may be of significance in the hemodynamics of fetal arterial circulation. (×180.)

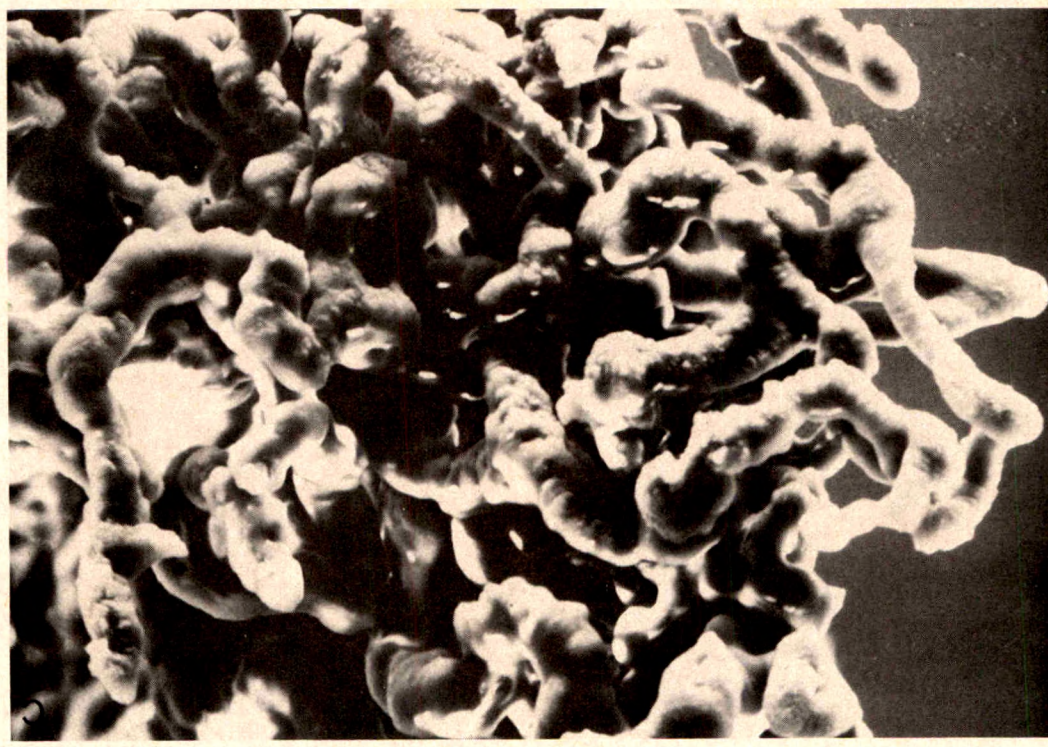


Fig. 5. Placental cast of fetal capillaries located at the arteriolar side of the blood supply. The dense capillary network has a markedly tortuous appearance. The luminal surfaces appear to be smooth, and the diameter of these small vessels are uniform in width. (×550.)



Fig. 6. Placental cast of venous side of fetal circulation. The capillary network (right) flows into venules and then into veins (left). The capillaries are no longer tortuous; instead, they are fairly straight in appearance. The blood is conducted directly from capillaries into larger venules and veins. (×120.)



Fig. 7. A higher power view of venous side capillary network showing the essentially straight course of the small caliber vessels. The direction of flow is downward (left) toward venules. The minor pits and elevations seen on the surface contour indicate that the endothelial lining of the venous side vessels is irregularly smooth. (×210.)

mitochondria, some rough endoplasmic reticulum, and a few vesicles. One endothelial cell may be attached to an adjacent one by tight junctions at the apposed surfaces. The cytoplasm is usually thinly stretched around the capillary lumen, forming a relatively smooth surface contour. A well-defined basement membrane surrounds the endothelial cells (Fig. 8). This figure also illustrates the close attachment of two pericytes to the outer surface of the endothelial cells. This close apposition of pericytes to the capillary wall, leaving no space in between, was observed frequently. On the lower left of Fig. 8, the inner trophoblast cell layer can be seen lying adjacent to the basement membrane of the fetal capillary. The cytoplasm of this inner layer of trophoblast contains lipid droplets which are fairly numerous here.

The venules observed in placental tissue have a fairly wide lumen with several endothelial cells forming the lining. The cytoplasm, while attenuated, is not as smooth as the lining of capillaries. The venules have a delicately irregular endothelial lining (Fig. 9) with small bleb-like structures projecting into the lumen, and surrounding the endothelial cells in a thin basement membrane.

During the course of transmission electron microscopic examination, we discovered a capillary with fetal erythrocyte (RBC) apparently being extruded through a minute opening in the endothelial wall (Fig. 10). The fetal RBC, containing several mitochondria, was wedged between two adjacent endothelial cells and was evidently about to enter the maternal blood space and mix with maternal red blood cells.

Comment

The placental circulation in rodents has been examined by various procedures through our corrosion-cast preparations supported by TEM observations. A higher degree of ultrastructual accuracy in the examination of the fetal microcirculation of rat placenta has been attained than has been possible with previous techniques.

To study placental morphology and functions, several significant injection studies have been done on rat placenta. In 1950, Bøe[4] did a series of experiments on placental circulation in rats, using first India ink injections and then corrosion preparations made with vinyl acetate. By means of these two types of injection techniques, Bøe demonstrated the vascular pattern of both fetal and maternal circulations. Our latex cast specimens of rat fetal blood vessels are in accord with the macroscopic vascular pattern demonstrated by his work.

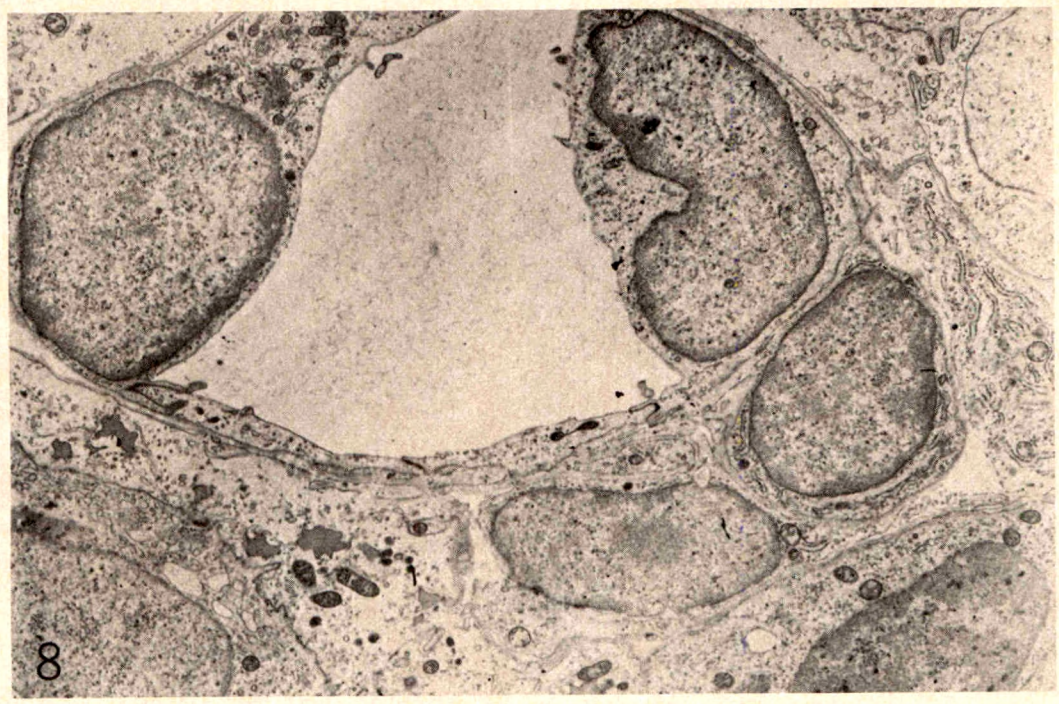


Fig. 8. Transmission electron micrograph of a fetal capillary from rat placenta. Two endothelial cell nuclei are evident; the attenuated endothelial cytoplasm forms a smooth lining. Tight junctions are located at the lateral surfaces which help to maintain close cell to cell contact. A thin basement membrane surrounds the endothelial cells. On the lower right, two pericytes lie in close apposition to the capillary wall. On the lower left, the inner layer of trophoblast is seen with lipid droplets present in the cytoplasm. (×5,250.)

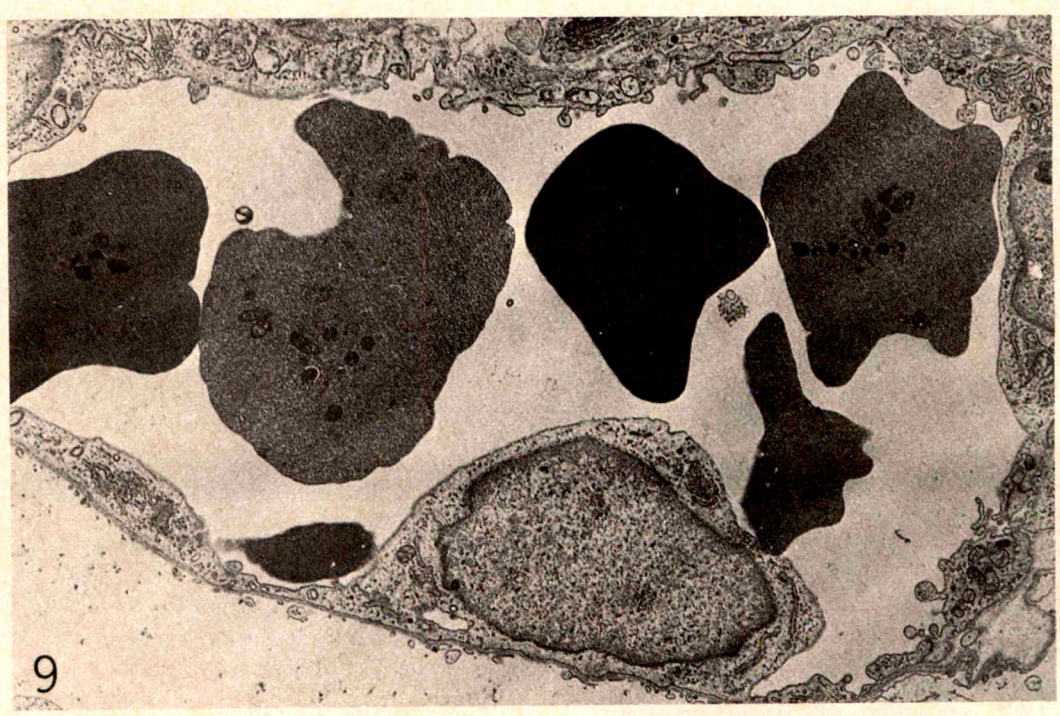


Fig. 9. Transmission electron micrograph of a fetal venule (near a capillary-venule junction) containing red blood corpuscles, several of which contain mitochondria. The lining of the venule has a slightly irregular surface; the endothelial cell cytoplasm sends many small bleb-like projections into the lumen. (×5,000.)



Fig. 10. Transmission electron micrograph showing a small capillary with a fetal erythrocyte protruding through a minute rupture in the endothelial wall. The fetal RBC was apparently leaving the capillary to enter into the maternal circulation; this ultrastructural evidence suggests that the placenta is not a tight seal. The leakage of fetal erythrocyte into the maternal circulation was not observed frequently. (×7,950.)

The investigations of Bøe and of Mossman provided evidence that the rodent placenta has a counter-current flow: i.e., the direction of blood flow in maternal and fetal blood vessels is in opposite directions. Our present anatomical findings are consistent with this concept; such a counter-current flow would provide a more efficient exchange of materials between mother and fetus, with gaseous and nutritive exchanges occurring in the dense capillary regions. Mossman[9] in his 1965 paper has discussed the various blood flow systems in mammalian placentas and concluded that the counter-current type may predominate. This would appear to contradict physiologic evidence presented by Meschia and associates[10] and by Wilkin[11] that the blood flow in sheep placenta is of the concurrent type. Their physiologic data indicated that a concurrent flow system exists in mammalian placentas and also that this type of blood flow provides for a less efficient diffusion rate between blood vessels. The counter-current flow theory of Mossman, however, does not entirely contradict the work of Meschia and associates since, in monkey and human placentas, the counter-current flow is restricted to only a limited area of the organ: i.e., significant counter-current flow occurs only in the short villi of the terminal tufts of the placenta where the delicate capillaries are of short length (0.2 to 0.7 mm.) and where the intervillous maternal blood interstices are about 1 mm. or less. The larger blood vessels of the placenta may operate on a concurrent system. So mammalian placentas may exhibit both types of blood flow in the same organ; or, they may be exclusively of one type throughout. While current physiologic data support a concurrent flow sytem in most mammalian placentas, some plascentas (e.g., rodent) remain of the counter-current type. Further anatomical studies in conjunction with physiologic findings would be helpful in elucidating the intricate patterns of placental blood flow.

SEM observations demonstrated that the capillaries in rat placenta are of fairly uniform diameter, with relatively smooth surface contours. This differs from the appearance of capillaries in rhesus monkey and in human placenta where Arts and Lohman[6] and Bøe[13] found the capillaries to be of varying caliber with sinusoidal dilatations. The difference, however, may be procedural for our injections were performed on anesthetized animals (with fetuses still alive) so that the resulting casts should show the fetal placental circulation with minimum alterations, if any, in the vasculature.

An unexpected observation was seen during SEM examination of the casts of fetal arteries. These large vessels are capable of sending off very small branches directly from the main stem. It would seem that such delicate branching from a large vessel is hemodynamically unfeasible, for the intravascular pressure within the artery must be relatively high, and at the division point of the small branch, such a pressure should be great enough to burst the delicate branch. A compensatory mechanism apparently exists to prevent vascular damage; however, no attempt was made to elucidate the intravascular pressure-regulating mechanism.

The SEM has also shown that the capillaries at the arteriolar side differ in appearance from those at the venous side. The first capillary network has a markedly tortuous appearance with numerous anastomoses present. This dense, tortuous capillary network located at the arteriolar end may have functional significance. Their winding and twisting course could reduce the velocity of the blood flow and hence facilitate the exchange processes which occur at the capillary level. Then, as this network forms anastomoses with the venous-side capillary network, the need for slow circulation of blood to facilitate absorption is decreased, while the need for faster drainage of blood is increased. Thus, the second capillary network has straighter vessels, all radiating towards the venules, carrying the blood directly into the collecting venules and veins. Morphology and function would appear to correlate quite well. While we have not yet examined casts of primate placenta in the SEM, we may speculate that such a similar ultrastructural vascular pattern would exist there also.

Electron microscopy of the human placenta has been done by many investigators.[12] Electron microscopy of rodent placenta also has been done.[14] These investigators have examined trophoblast cells, syncytium, and capillary tissues. Our present findings confirm and extend previous electron microscopic observations. The capillary wall is composed of endothelial cells with attenuated cytoplasm attached at one cell surface to another by tight junctions which serve to maintain close cell-to-cell contact. A well-defined basement membrane surrounds the capillaries and, quite often, pericytes are found closely applied to the outside of endothelial cells. In addition to these observations, we have described the appearance of venules and also the appearance of a fetal erythrocyte apparently leaving a capillary through a minute rupture in the endothelial wall. The occasional leakage of fetal erythrocytes into the maternal circulation has been postulated as an explanation for erythroblastosis fetalis and has been examined by experimental work in physiology,[15] but not previously visualized by electron microscopy. Our observations provide physical evidence of the possibility that fetal erythrocytes can leave capillaries to enter the maternal circulation.

A final word remains to be said about the significance of utilizing the SEM to recognize and to interpret the vascular pattern of the placenta. To date, SEM observations of the placenta have been limited mainly to surface examination, expecially of the villi.[7] Sheppard and Bonnar[8] initiated SEM studies on placental blood vessels, including spiral arteries. Our present report examines the blood vessels in the SEM by a different technique. Both methods could be applied to the study of placental vasculature to expand our knowledge of fetal and maternal circulation within the placenta. We have seen that the two microscopic techniques could be correlated. The ultrastructural findings of TEM support SEM observations as demonstrated, for example, by the smooth luminal surfaces of capillary casts accurately representing the smooth endothelial lining seen in the TEM. Similarly, the irregular endothelial lining seen in the TEM of fetal venules caused minor pits and elevations to be present in the venule cast specimens. In the same manner infarcts, thrombi and fibrin depositions observable in the TEM would, depending on degree of severity, be visualized as partial to complete constrictions in cast specimens seen in the SEM. An examination of the pattern of distribution of vascular lesions such as infarcts and thrombi may reveal the cause of some cases of fetal morbidity and death. The corrosion-cast technique coupled with TEM observations can illuminate the ultrastructural pathologic changes which may occur in the placental circulation during maternal disease states or during drug administration. Our findings suggest that this procedure will be applicable to such future studies on the placenta as they have done previously in studies on the experimentally altered kidney.

The advice and help of Drs. Myron Tannebaum and Richard Hoar is acknowledged with appreciation.

REFERENCES

1. Lee, M. L., Purkerson, M. L., Agate, F. J., and Dempsey, E. W.: Ultrastructural changes in renal glomeruli of rats during experimentally induced hypertension and uremia, Am. J. Anat. **135:** 191, 1972.
2. Lee, M. L.: Morphological effects of procaine amide on

mouse kidney as observed by scanning and transmission electron microscopy, Lab. Invest. **31:** 324, 1974.
3. Nowell, J. A., and Lohse, C. L.: Injection replication of the microvasculature for scanning electron microscopy, *in* Johari, O., and Corvin, I., editors: Scanning Electron Microscopy/1974, Chicago, 1974, ITT Res. Inst., pp. 267-271.
4. Bøe, F.: Studies on placental circulation in rats. II. Vascular pattern illustrated by corrosion preparations, Acta. Endocrinol. **5:** 369, 1950.
5. Arts, N. F. Th.: Investigation on the vascular system of the placenta, Am. J. Obstet. Gynecol. **82:** 147, 1961.
6. Arts, N. F. Th., and Lohman, A. H. M.: An injection-corrosion study of the fetal and maternal vascular systems in the placenta of the rhesus monkey, Eur. J. Obstet. Gynecol. Reprod. Biol. **4:** 133, 1974.
7. Ludwig, H.: Surface structure of the human term placenta and of the uterine wall post partum in the screen scan electron microscope, Am. J. Obstet. Gynecol. **111:** 328, 1971.
8. Sheppard, B. L., and Bonnar, J.: Scanning electron microscopy of the human placenta and decidual spiral arteries in normal pregnancy, J. Obstet. Gynaecol. Br. Commonw. **81:** 20, 1974.
9. Mossman, H. W.: The principal interchange vessels of the chorioallantoic placentas of mammals, *in* DeHaan, R. L., and Ursprung, H., editors: Organogensis, New York, 1965, Holt, Rinehart & Winston, pp. 771-785.
10. Meschia, G., Battaglia, F. C., and Bruns, P. D.: Theoretical and experimental study of transplacental diffusion, J. Appl. Physiol. **22:** 1171, 1967.
11. Wilkin, P.: Les théories explicatives du mécanisme des échanges transplacentaires, *in* Snoeck, J., Editor: Le Placenta Humain, Paris, 1975, Masson et Cie., pp. 238-279.
12. Martinek, J. J., Gallagher, M. L., and Essig, G. F.: An electron microscopic study of fetal capillary basal laminas of 'normal' human term placentas, Am. J. Obstet. Gynecol. **121:** 17, 1975.
13. Bøe, F.: Studies on human placenta. III. Vascularization of the young fetal placenta. B. Vascularization of the translucent villus and the syncytial band, with special reference to the cell islands and the basal plate, Acta Obstet. Gynecol. Scand. **48:** 167, 1969.
14. Wislocki, G. B., and Dempsey, E. W.: Electron microscopy of the placenta of the rat, Anat. Rec. **123:** 33, 1955.
15. Dancis, J., and Schneider, H.: Physiology: Transfer and barrier function, *in* Gruenwald, P., Editor: The Placenta and Its Maternal Supply Line, Univ. Baltimore, 1975, University Park Press.

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Case of ovarian dropsy, successfully removed by a surgical operation

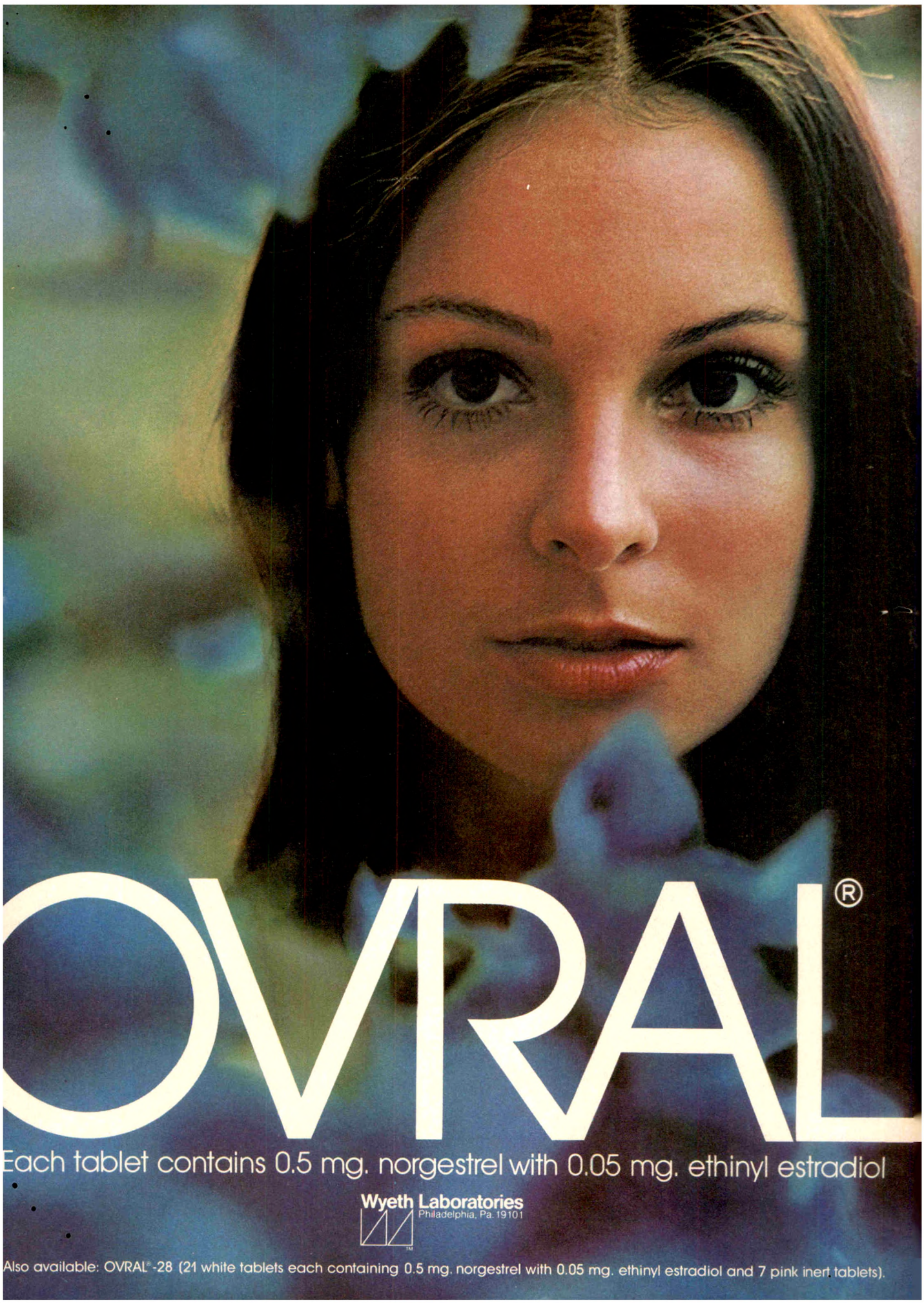
NATHAN SMITH
American Medical Recorder, vol. 5, pp. 124-126, 1822

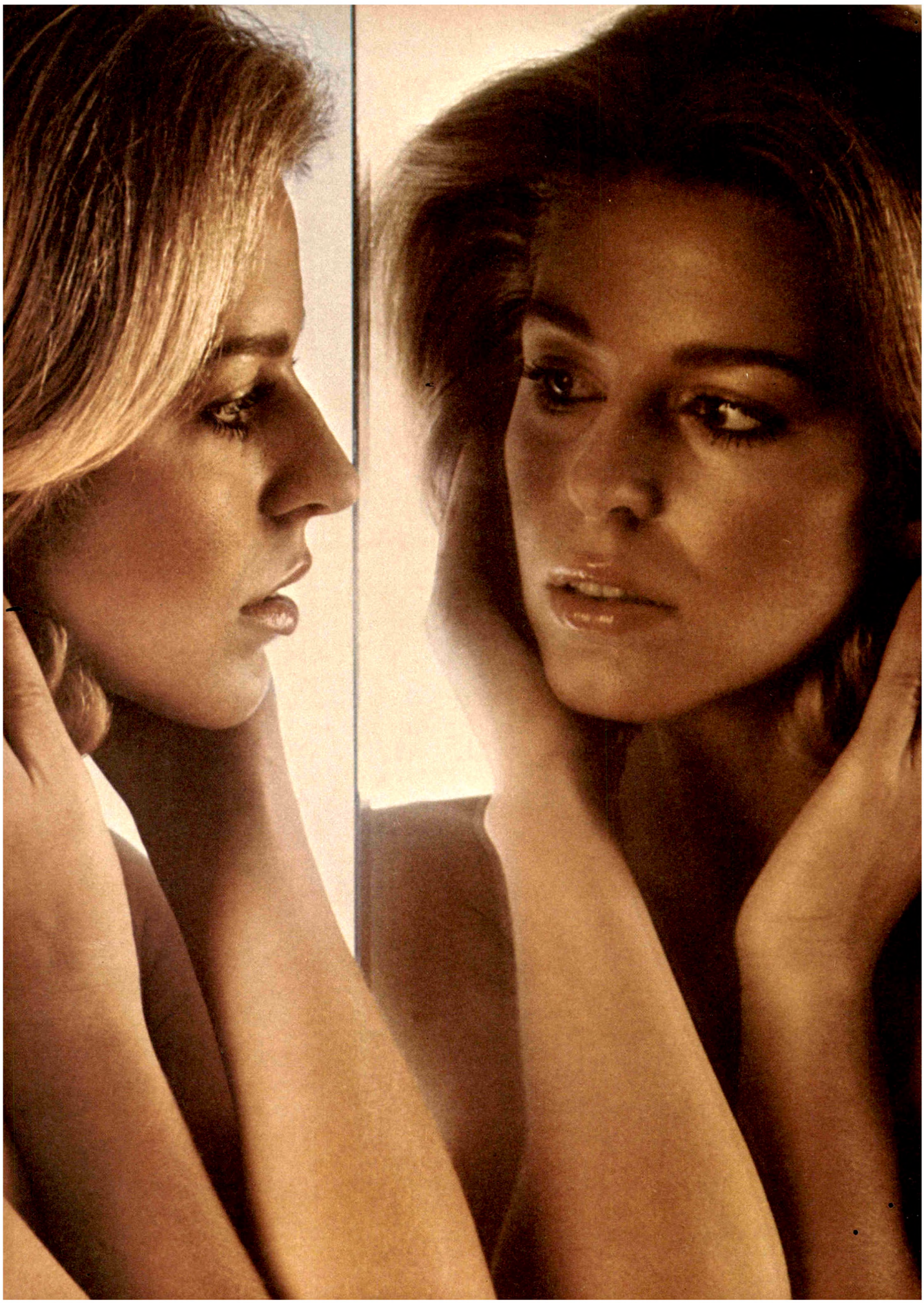
adhering to it, a considerable portion of the omentum. This was separated from the sack with the knife; and two arteries, which we feared might bleed, were tied with leather ligatures, and the omentum was returned. By continuing to pull out the sack, the ovarian ligament was brought out, this was cut off, two small arteries, secured with leather ligatures, and the ligament was then returned. I then endeavoured to separate the sack from its adhesions to the parietes of the abdomen, which occupied a space about two inches square; this was affected by a slight stroke of the knife at the anterior part of the adhesion, and by use of the fingers. The sack then came out whole, excepting where the juncture was made, and I should think it might weigh between 2 and 4 ounces. The incision was then closed with adhesive plaster, and a bandage applied over the abdomen. No unfavourable symptoms occurred after the operation; in three weeks the patient was able to sit up and walk, and has since perfectly recovered.

I was induced to undertake this operation from the following considerations:—The patient, though her health was not greatly impaired, was sensibly affected by the disease. She was quite certain that the increase of the tumour, in a given time, was augmented; probably, at no very distant period, it would destroy her. I had, also, an opportunity to dissect the body of a patient, who had died of ovarian dropsy, after being tapped seven times. In this case the sack was found to be in the right ovarium, which filled the whole abdomen; but it adhered to no part except the proper ligament, which was not larger than the finger of a man. I have seen two other ovarian sacks which were taken from patients after death. They had been tapped several times; the sacks were equally unattached, except to their own proper ligaments. Hence, I inferred, that in a case of ovarian dropsy, while the tumour remained moveable, it might be removed with a prospect of success. The mode of operating, practised in the above case, is the same as I have described to my pupils in several of my last courses of lectures on surgery. The event has justified my previous opinions.

*** The author, at the time of reporting the above case, was ignorant that Dr. Dzondi had proposed the attempt to cure ovarian dropsy by the introduction of a tent following puncture, that the dropsical sack might slough, and be withdrawn by forceps.—Vid. Medical Recorder, Vol. III. p. 63.

Smith, professor of physic and surgery at Yale, was the first in the United States, after Ephraim McDowell, to successfully perform oophorectomy. He apparently did not know of McDowell's report. The patient was 33 years old and seven years previously had noticed a freely movable tumor the size of a goose egg in the right iliac region. She had two children prior to that time and three afterward. During the course of these pregnancies, the cyst apparently ruptured twice, disappearing for a few weeks, only to return. It also ruptured following a fall but on reappearing the third time steadily increased in size. Finally it was so large that it ". . . incommoded her in the ordinary duties of her family, especially in stooping." With an assistant holding the tumor in the middle of the abdomen, Smith made an infraumbilical midline incision. After drawing off over seven pints of fluid, he exteriorized the cyst wall and adherent omentum (continued in the illustration). He ligated the ovarian pedicle with fine strips of leather cut from a kid glove. Smith anticipated modern surgical technique by cutting the sutures short, dropping them back into the abdominal cavity, and completely closing the abdomen, in contrast to exteriorizing them or suturing them to the abdominal wall as was practiced by others. Smith, a pioneer in American medicine, was foremost a surgeon and teacher. A peripatetic organizer of medical schools, he played an important role in founding Dartmouth and Yale and also was involved in the organization of Bowdoin Medical School, University of Maine; Burlington Medical School, University of Vermont; and the Thomas Jefferson Medical College in Philadelphia. (Photograph courtesy of the National Library of Medicine.)


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol
Wyeth Laboratories
Philadelphia, Pa. 19101
Also available: OVRAL®-28 (21 white tablets each containing 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol and 7 pink inert tablets).



Predictably Duplicates Her Natural Thyroid Hormone Requirements

SYNTHROID® (Sodium Levothyroxine, U.S.P.) Flint is T4 . . . and it is chemically pure, containing no animal gland components. This simply means that you can depend upon the hormone content being of controlled potency, batch after batch.

SYNTHROID is a pure synthetic and identical to the principal secretion of the normal thyroid gland.

SYNTHROID medication provides your patients with everything they need for complete thyroid replacement therapy. It is the most widely prescribed brand name of thyroid in the United States and Canada.

T4 (SYNTHROID) converts to T3 at the cellular level, providing full thyroid replacement at maintenance doses.[1,2]

SYNTHROID®
(Sodium Levothyroxine, U.S.P.) Flint

See reverse side for full prescribing information

Consider, too, that T4 (SYNTHROID) replacement therapy assures uniform levothyroxine dosage and simplifies monitoring the dosage regimen.

Available now for a limited time only —a handy reference book with up-to-date information on thyroid function tests. Written in consultation with a number of leading endocrinologists, this reference book can be obtained by writing Flint Laboratories or contacting your Flint representative. We appreciate the opportunity to be of service.

1. Braverman, L. E., Ingbar, S. H., and Sterling, K. Conversion of Thyroxine (T4) to Triiodothyronine (T3) in Athyreotic Human Subjects. J. Clin. Invest. 49:855-64, 1970.
2. Surks, M. I., Schadlow, A. R., and Oppenheimer, J. H. A New Radioimmunoassay for Plasma L-Triiodothyronine: Measurements in Thyroid Disease and in Patients Maintained on Hormonal Replacement. J. Clin. Invest. 51:3104-13, 1972.

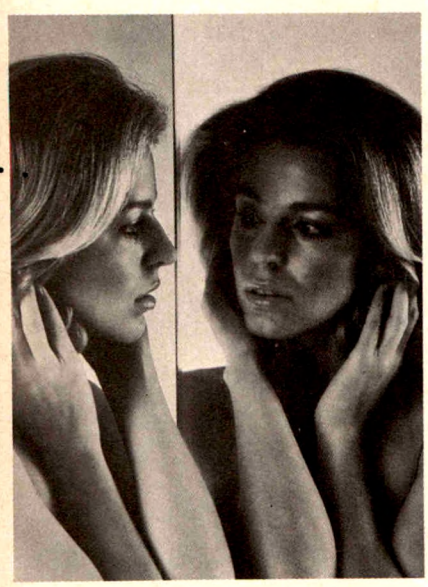


FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

SYNTHROID®

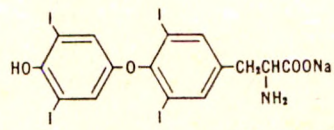
(Sodium Levothyroxine, U.S.P.) Flint

Provides Complete Thyroid Replacement Therapy



Synthroid Tablets—for oral administration
Synthroid for Injection—for parenteral administration

Description: SYNTHROID (sodium levothyroxine) **Tablets** and SYNTHROID **Injection** contain synthetic crystalline sodium levothyroxine (L-thyroxine). L-thyroxine is the principal hormone secreted by the normal thyroid gland.



Sodium Levothyroxine

Actions: SYNTHROID (sodium levothyroxine) **Tablets,** taken orally, provide hormone that is readily absorbed from the gastrointestinal tract. SYNTHROID **Injection** is effective by any parenteral route. Following absorption, the synthetic L-thyroxine provided by SYNTHROID products cannot be distinguished from L-thyroxine that is endogenously secreted. Each is bound to the same serum proteins and each exhibits a six to seven day circulating half-life in the euthyroid individual.

Both SYNTHROID products will provide L-thyroxine as a substrate for physiologic deiodination to L-triiodothyronine. Therefore, patients taking SYNTHROID products will demonstrate normal blood levels of L-triiodothyronine even when the thyroid gland has been surgically removed or destroyed by radioiodine. Administration of levothyroxine alone will result in complete physiologic thyroid replacement.

Indications: SYNTHROID (sodium levothyroxine) products serve as specific replacement therapy for reduced or absent thyroid function of any etiology. SYNTHROID **Injection** can be used intravenously whenever a rapid onset of effect is critical, and either intravenously or intramuscularly in hypothyroid patients whenever the oral route is precluded for long periods of time.

Contraindications: There are no absolute contraindications to SYNTHROID (sodium levothyroxine) therapy. Relative contraindications include acute myocardial infarction, uncorrected adrenal insufficiency and thyrotoxicosis. (See WARNINGS)

Warnings: Patients with cardiovascular diseases warrant particularly close attention during the restoration of normal thyroid function by any thyroid drug. In such cases, low initial dosage increased slowly by small increments is indicated. Occasionally, the cardiovascular capacity of the patient is so compromised that the metabolic demands of the normal thyroid state cannot be met. Clinical judgment will then dictate either a less-than-complete restoration of thyroid status or reduction in thyroid dosage.

Endocrine disorders such as diabetes mellitus, adrenal insufficiency (Addison's disease), hypopituitarism and diabetes insipidus are characterized by signs and symptoms which may be diminished in severity or obscured by hypothyroidism. SYNTHROID (sodium levothyroxine) therapy for such patients may aggravate the intensity of previously obscured symptoms and require appropriate adjustment of therapeutic measures directed at these concomitant disorders.

Thyroid replacement may potentiate the effects of anticoagulants. Patients on anticoagulant therapy should have frequent prothrombin determinations when instituting thyroid replacement to gauge the need to reduce anticoagulant dosage.

Precautions: Overdosage with any thyroid drug may produce the signs and symptoms of thyrotoxicosis, but resistance to such factitious thyrotoxicosis is the general rule. With SYNTHROID (sodium levothyroxine) **Tablets,** the relatively slow onset of action minimizes the risk of overdose but close observation in the weeks following institution of a dosage regimen is advised. Treatment of thyroid hyperactivity induced by oral medication is confined to interruption of therapy for a week, followed by reinstitution of daily therapy at an appropriately reduced dosage.

Adverse reactions: Adverse reactions are due to overdose and are those of induced hyperthyroidism.

Dosage and administration: For most adults, a final dosage of 100 mcg (0.1 mg) to 200 mcg (0.2 mg) of SYNTHROID (sodium levothyroxine) **Tablets** daily will restore normal thyroid function and only occasionally will patients require larger doses. Failure to respond adequately to a daily oral intake of 400 mcg (0.4 mg) or more is rare and should prompt reconsideration of the diagnosis of hypothyroidism, special investigation of the patient in terms of malabsorption of L-thyroxine from the gastrointestinal tract or poor adherence to therapy.

The concomitant appearance of other diseases, especially cardiovascular diseases, usually dictates a replacement regimen with initial doses smaller than 100 mcg/day (0.1 mg).

In otherwise healthy adults with relatively recent onset of hypothyroidism, full replacement dose of 150 mcg (0.15 mg) or 200 mcg (0.2 mg) has been instituted immediately without untoward effect and with good therapeutic response. General experience, however, favors a more cautious approach in view of the possible presence of subclinical disorders of the cardiovascular system or endocrinopathies.

The age and general physical condition of the patient as well as the severity and duration of hypothyroid symptoms determine the starting dosage and the rate of incremental dosage increase leading to a final maintenance dosage. In the elderly patient with long standing disease, evidence of myxedematous infiltration and symptomatic, functional or electrocardiographic evidence of cardiovascular dysfunction, the starting dose may be as little as 25 mcg (0.025 mg) per day. Further incremental increases of 25 mcg (0.025 mg) per day may be instituted at three to four week intervals depending on patient response. Conversely, otherwise healthy adults may be started at higher daily dosage and raised to the full replacement dosage in two to three weeks. Clearly it is the physician's judgment of the severity of the disease and close observation of patient response which determines the rate of dosage titration.

Laboratory tests to monitor thyroid replacement therapy are of limited value. Although measurement of normal blood levels of thyroxine in patients on replacement regimens frequently coincides with the clinical impression of normal thyroid status, higher than normal levels on oral replacement of levothyroxine occasionally occur and should not be considered evidence of overdosage per se.

In all cases, clinical impression of the well-being of the patient takes precedence over laboratory determination in determining the appropriate individual dosage.

In infants and children, there is a great urgency to achieve full thyroid replacement because of the critical importance of thyroid hormone in sustaining growth and maturation. Despite the smaller body size, the dosage needed to sustain a full rate of growth, development and general thriving is higher in the child than in the adult, as much as 300 mcg (0.3 mg) to 400 mcg (0.4 mg) per day.

In myxedema coma or stupor, without concomitant severe heart disease, 200 to 500 mcg of SYNTHROID **Injection** may be administered intravenously as a solution containing 100 mcg/ml. Although the patient may show evidence of increased responsivity within six to eight hours, full therapeutic effect may not be evident until the following day. An additional 100 to 300 mcg or more may be given on the second day if evidence of significant and progressive improvement has not occurred. Like the oral dosage form, SYNTHROID **Injection** produces a predictable increase in the circulating level of hormone with a long half-time. This usually precludes the need for multiple injections but continued daily administration of lesser amounts intravenously should be maintained until the patient is fully capable of accepting a daily oral dose.

In the presence of concomitant heart disease, the sudden administration of such large doses of L-thyroxine intravenously is clearly not without its cardiovascular risks. Under such circumstances, intravenous therapy should not be undertaken without weighing the alternative risks of the myxedema coma and the cardiovascular disease. Clinical judgment in this situation may dictate smaller intravenous doses of levothyroxine.

SYNTHROID **Injection** by intravenous or intramuscular routes can be substituted for the oral dosage form when ingestion of SYNTHROID **Tablets** is precluded for long periods of time.

How Supplied: SYNTHROID (sodium levothyroxine) **Tablets** are supplied as scored, color-coded compressed tablets in 6 concentrations: 25 mcg (0.025 mg)—orange . . . 50 mcg (0.05 mg)—white . . . 100 mcg (0.1 mg)—yellow . . . 150 mcg (0.15 mg)—blue . . . 200 mcg (0.2 mg)—pink . . . 300 mcg (0.3 mg)—green.

SYNTHROID (sodium levothyroxine) for **Injection** is supplied in 10 ml vials containing 500 mcg of lyophilized active ingredient and 10 mg of Mannitol, U.S.P. A separate 5 ml vial containing Sodium Chloride Injection, U.S.P. is provided as a diluent.

Directions for reconstitution: Reconstitute the lyophilized sodium levothyroxine by aseptically adding 5 ml of the Sodium Chloride Injection, U.S.P. to the vial. Shake vial to insure complete mixing. **Use immediately** after reconstitution. Discard any unused portion.

U.S. Pat. 2,889,363

January 1975

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015



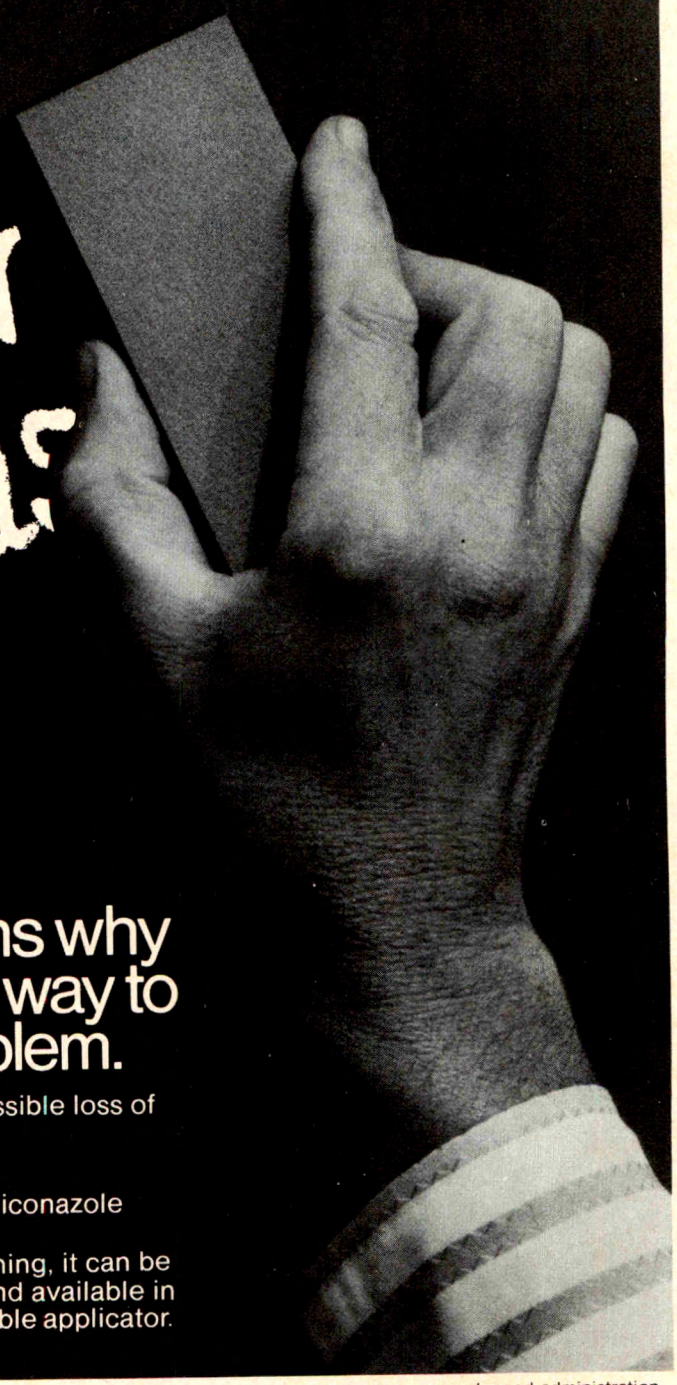
NEW & BETTER

...The all-American Frigi Colposcope

- At half the cost of comparable imports, even including the cost of teaching tube and camera adaptor.
- Superior to the finest German and Japanese models.
- Plus, choices and options to suit your practice.
- Plus sales and service representation in your locale.
- Seeing is believing. See it in your office. Call collect today.

frigitronics®
OF CONNECTICUT INCORPORATED
770 RIVER ROAD, SHELTON, CONNECTICUT 06484
203/929-6321

KOROSTATIN
...(Nystatin Tablets U.S.P.)



Vulvovagir Candidia

There are a lot of reasons why Korostatin is the better way to eliminate a serious problem.

- NO REFRIGERATION NEEDED...Eliminates possible loss of potency at room temperature
- EFFICACY...A proven specific
- ECONOMY...Dramatically less expensive than miconazole nitrate cream
- ADDITIONAL BENEFITS...Korostatin is nonstaining, it can be used throughout pregnancy, it is well tolerated and available in convenient 14 and 28 tablet packages, with reusable applicator.

DESCRIPTION: KOROSTATIN (Nystatin) Vaginal Tablets, U.S.P. is in an oblong shaped vaginal tablet, each containing 100,000 units of Nystatin, U.S.P. Inactive ingredients include: starch, lactose, polyvinylpyrrolidone, sorbitol and magnesium stearate.

INDICATIONS FOR USE: KOROSTATIN (Nystatin) Vaginal Tablets U.S.P. are indicated in the local treatment of vulvovaginal candidiasis.

CONTRAINDICATIONS: All Nystatin preparations are contraindicated in patients with a history of hyper-sensitivity to Nystatin.

ADVERSE REACTIONS: Nystatin, U.S.P. is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even on prolonged administration. If irritation during intravaginal use should occur, discontinue the medication.

For full prescribing information, consult package insert.

KOROSTATIN is manufactured under Holland-Rantos specifications by the American Cyanamid Company.

HOLLAND-RANTOS CO., INC.
P.O. Box 5, Piscataway, New Jersey 08854
Serving the need of the OB/GYN community for over 50 years.

Each tablet contains a low dosage of progestin, 1 mg norethindrone, and a low dosage of estrogen, 0.05 mg mestranol. Clinical studies with Ortho-Novum 1/50 show a pregnancy rate of only 0.26 per 100 woman years.

Low incidence of minor side effects† Experience shows a low incidence of discontinuance due to medication.

DIALPAK* Tablet Dispenser Designed for your patients' convenience, but more importantly, helps reduce the possibility of error through missed tablets. The unique DIALPAK dispensing system is patient preferred.††

†Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

most women who start with it stay with it

Ortho-Novum 1/50

Each yellow tablet contains 1 mg norethindrone and 0.05 mg mestranol. TRADEMARK □ 21 and 28
Each green tablet in the 28-day regimen contains inert ingredients.



See Prescribing Information on following page.

*TRADEMARK
††Burke Marketing Research, Inc.
©Ortho Pharmaceutical Corporation, 1976
OJ 277-6

Most women who start with it stay with it



Ortho-Novum 1/50 ☐21 and 28

TRADEMARK

Ortho-Novum 1/50 ☐21 and Ortho-Novum 1/50 ☐28

Description: Each ORTHO-NOVUM 1/50 ☐21 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol.

Each yellow ORTHO-NOVUM 1/50 ☐28 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol. Each green tablet contains inert ingredients.

Actions: ORTHO-NOVUM 1/50 ☐21 and ORTHO-NOVUM 1/50 ☐28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/50 ☐21 and ORTHO-NOVUM 1/50 ☐28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28. Therefore, if such tests are abnormal in a patient taking ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 may mask the onset of the climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol-extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J 2:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J 2:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health, 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.I.; Vessey, M.P.; Thorogood, M.; Doll, R.; Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J 2:241-245, May 3, 1975. **12.** Mann, J.I.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J 2:245-248, May 3, 1975. **13.** Nora, J.J.; Nora, A.H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291*(14):697-700, Oct. 3, 1974.

Ortho Pharmaceutical Corporation • Raritan, New Jersey 08869

Ortho

COMMUNICATIONS IN BRIEF

This section is suitable for reporting cases, results of therapeutic trials, and descriptions of new procedures or instruments. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

An unusual complication of tubal sterilization by silicone rubber banding under laparoscopic vision

JOHN M. ESPOSITO, M.D.

Department of Obstetrics and Gynecology, The Methodist Hospital, Brooklyn, New York

SILICONE banding of the Fallopian tube under laparoscopic vision is a technique developed to eliminate the dangers inherent in the use of electrosurgery, i.e., thermal injuries to the bowel and skin. Yoon and King[1] reported 500 cases of silicone rubber banding and had the following complications: two would infections, six tubal injuries, and one incisional hematoma of the periumbilical region. Only the six tubal injuries were related to the application of the band.

It is the purpose of this brief communication to report the inadvertent inclusion of a small knuckle of bowel with the Fallopian tube in the silicone band. The treatment of the complication and the steps to be taken to prevent it are discussed.

M. A., a 24-year-old woman, gravida 4, para 4, was admitted to The Methodist Hospital on July 28, 1975, for sterilization by silicone banding under laparoscopic vision. Her last menstrual period was July 19, 1975. The past and family history were noncontributory. Physical examination revealed a well-developed and well-nourished Puerto Rican woman whose physical findings were within normal limits. The uterus was anterior and mobile and normal in size, shape, and consistency. There were no adnexa masses and the cervix appeared healthy. The admitting diagnosis was multiparity. Preoperative laboratory data revealed a hemoglobin of 14.1 and a white blood count of 7,800, with a normal differential. Urinalysis was within normal limits. Serology was VDLR negative and the blood type was O positive. Chest examination showed no significant abnormalities.

The patient was taken to the operating room on July 29, 1975, and under laparoscopic vision silicone bands were applied to the Fallopian tubes. Application of the band to the right Fallopian tube proceeded without incident. After the application of the silicone ring to the left tube, it was noted that a small knuckle of bowel was included in the ring.

It was decided that the band must be removed. Instead of proceeding immediately to laparotomy, an attempt at removal under laparoscopic vision was made. Siegler forceps* were inserted through the second puncture trocar. Care was taken to grasp the ring in the area opposite to that which included the knuckle of intestines. The band was cut and remained in the jaws of the Siegler forceps. This freed the intestines and the left Fallopian tube. The band was then removed through the lateral trocar. The left Fallopian tube was grasped once again with the Falope-Ring applicator† and elevated so that there was no bowel seen in the immediate vacinity and the silicone tubal ring applied.

The patient's postoperative course was uneventful and she was discharged on July 31.

This is believed to be the first case reported in which a knuckle of bowel had been inadvertently included in the silicone ring at the time of its application to the Fallopian tube. In order to assure that this complication does not occur, it is wise to place the patient in adequate Trendelenberg position so that the intestines are displaced from the lesser pelvis. It is also necessary to tent the tube and to have an adequate view, thus assuring that it is completely isolated from other intraperitoneal contents prior to application of the silicone band.

This case demonstrates that silicone rings can be removed under laparoscopic vision without the necessity of proceeding to laparotomy. It would seem that the Siegler biopsy forceps is the ideal tool in this situation, since after the ring is cut it remains in the

Reprint requests: John M. Esposito, M.D., 246 86th St., Brooklyn, New York 11235.

*A.C.M.I., New York

†KLI Company, Ivgland, Pennsylvania.

jaws of the forceps, making possible its removal through the second puncture site.

REFERENCE

1. Yoon, I. B., and King, T. M.: A preliminary and intermediate report on a new laparoscopic tubal ring procedure, J. Reprod. Med. **15:** 54, 1975.

Cytogenetic studies in gonadal dysgenesis with dysgerminoma

ANTONIOS PSAROUDAKIS, M.D.*
MOSHE OETTINGER, M.D.*
J. ROGERS BYRD, PH.D.
ROBERT B. GREENBLATT, M.D.

Medical College of Georgia, Augusta, Georgia

GONADAL dysgenesis with female phenotype and male 46,XY karyotype is associated with a high incidence of gonadal tumors.[1] A classification of these gonadal neoplasms, based on the term "gonocytoma," was proposed by Teter in 1960. According to this classification, tumors containing germ cells are assigned to one of four groups, depending on the number of cell types and the endocrine properties of these cell types. Gonocytoma 1 is a homogenous type of tumor which is formed solely of germ cells, i.e., gonocytes, separated by a variable amount of collagenous tissue, and is synonymous with dysgerminoma—a name given by R. Meyer. This rare ovarian tumor is identical to seminoma found in the testicle.

Modern methods of cytogenetics have furnished more detailed information about these patients. Teter and Boczkowski[2] observed that whenever a germ cell tumor is found in a dysgenetic gonad, a Y chromosome is present.

The aim of the present communication is to report the cases of two patients, both suffering from gonocytoma 1—dysgerminoma, in whom a cytogenetic workup proved of great importance in diagnosis and management.

A 15-year-old girl presented with typical features of Turner's syndrome. Buccal smear was negative for Barr's sex chromatin. Cytogenetic studies on peripheral blood leukocytes revealed mosaicism with 96 per cent of cells 45,X (Fig. 1) and 4 per cent of cells 46,XY (Fig. 2). Fifty cells were counted, out of which 48 contained 45 chromosomes and two cells contained 46 chromosomes. C-banding revealed a Y chromosomes in those cells with 46 chromosomes. At laparotomy an infantile uterus was found. The left gonad was replaced by a large tumor mass, 7 by 5 by 2½ cm., firm in consistency, and covered by a gray, glistening, smooth capsule. There were a few nodules in some areas of the tumor, measuring approximately 1.5 cm. in largest diameter. The right gonad was small, somewhat thicker than the usual rudimentary streak. Both adnexa were surgically removed.

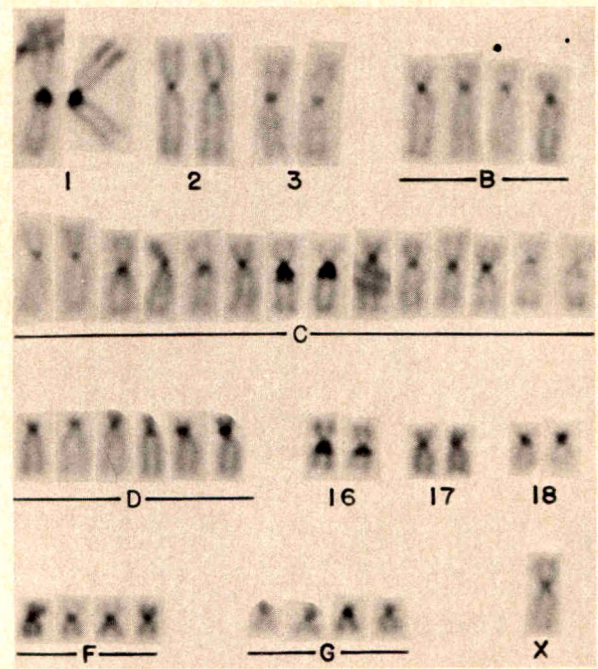


Fig. 1. Patient No. 1. Karyotype showing 45,X. C-banded.

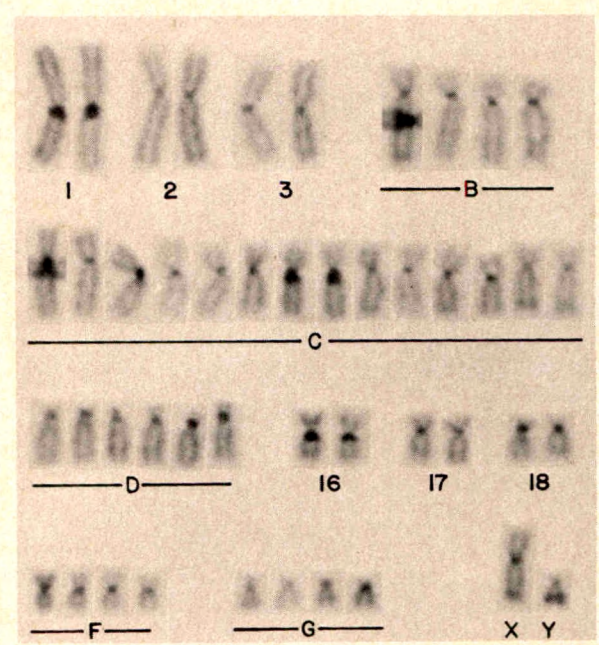


Fig. 2. Patient No. 1. Karyotype showing 46,XY. C-banded.

Reprint requests: Robert B. Greenblatt, M.D., Department of Endocrinology, Medical College of Georgia, Augusta, Georgia 30902.

*Research Fellows, Department of Endocrinology.

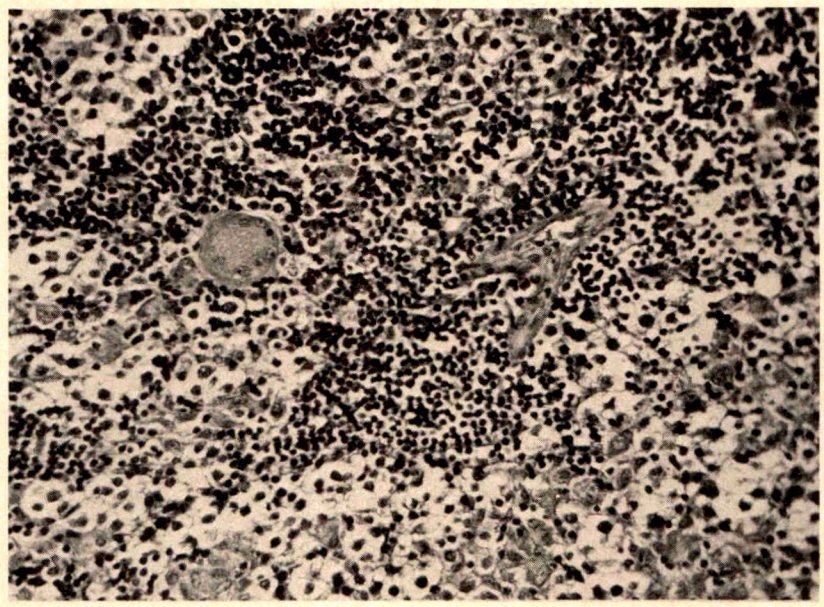


Fig. 3. Patient No. 2. Photomicrograph of histologic section of dysgerminoma of left ovary showing giant cell.

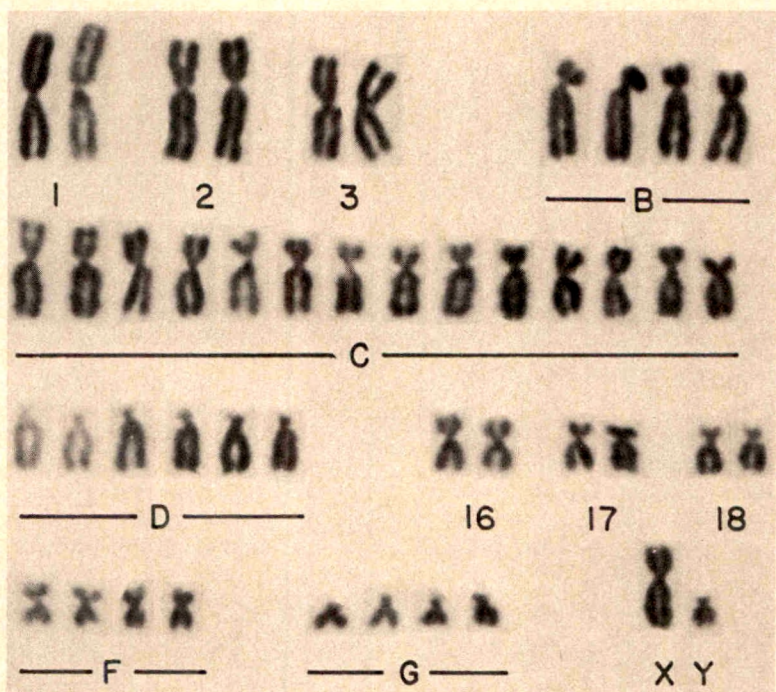


Fig. 4. Patient No. 2. Karyotype showing 46,XY.

The microscopic pathology was as follows: the right gonad lacked ovarian differentiation. Its stroma was composed of compact cells resembling fibroblasts. A prominent feature was multiple foci of calcifications deep in the stroma, some of them surrounded by cells resembling theca cells. In these areas there were also structures having resemblance to follicles with theca and granulosa cells. These structures suggested an attempt at follicle formation with degenerative changes in which calcification occurred. Section of the left tumor revealed a dysgerminoma with typical groups of round ovoid tumor cells separated by delicate fibro-

October 15, 1976
Am. J. Obstet. Gynecol.

lymphoid stroma. In these cells, focal necrosis was found.

A 19-year-old white female patient presented with primary amenorrhea. The breasts were underdeveloped and the pubic and axillary hair was very scant. Examination revealed a normal clitoris with slightly underdeveloped labia; a small uterus was felt on pelvic examination but the ovaries were not palpable. The vaginal smear was of the castrate type.

FSH and LH radioimmunoassay determinations for 3 consecutive days gave values of 50 mI.U. per milliliter for FSH, and 9.9, 11.9 mI.U. per milliliter for LH. Buccal epithelial cells were negative for Barr's sex chromatin mass.

A diagnosis of gonadal dysgenesis was made and an exploratory laparotomy was performed. Bilateral streak gonads were found, the left one thicker than the right one. On the left gonad there was a small 2 by 1 by 2 cm., irregular, firm nodule which was excised and biopsies were obtained from both streak gonads.

The description of the microscopic pathology was as follows: sections from the left gonadal nodule revealed a dysgerminoma; the histology was quite typical, consisting of large primitive germ cell types and small mature lymphocytes. In some areas of the tumor there was a definite epithelioid reaction with the formation of giant cells (Fig. 3). The specimen from the left gonad showed dysgenesis. In this gonad there were several collections of cells in the hilum which probably originated from the dysgerminoma. They were large clear cells and in one area there was a tuberculoid reaction. The specimen from the right gonad showed dysgenesis. No ova were found.

Following the exploratory laparotomy, cytogenetic studies on peripheral leukocytes showed the patient's karyotype to be 46,XY, not different from that of a normal male (Fig. 4). Thirty-nine cells were counted. Three cells contained 45 chromosomes and 36 cells had 46 chromosomes. Ten cells were karyotyped, seven of which were 46,XY. The other three cells with 45 chromosomes had dissimilar chromosomes missing, indicating artifactual random loss rather than chromosome mosaicism. Subsequent to the histologic findings, panhysterectomy was undertaken.

We conclude that: (1) there is an association between male karyotype and gonocytoma 1—dysgerminoma; (2) it is possible to find dysgerminoma in mosaics with 45,X chromosomal pattern and minimal occurrence of XY, hence the importance of counting large numbers of cells in cytogenetic studies; (3) all amenorrheic patients with an XY karyotype—pure or in mosaic form—should be explored for the existence of germ cell tumors in the gonads. In all XY cases it is recommended that the gonads be extirpated.

REFERENCES

1. Collins, J. C., and Schoenenberger, A. P.: J. Urol. **87:** 710, 1962.
2. Teter, J., and Bocskowski, K.: Cancer **20:** 1301, 1967.

Gonococcal sepsis secondary to fetal monitoring

HARAGOPAL THADEPALLI, M.D.
KAMALAKAR RAMBHATLA, M.D.
JACK E. MAIDMAN, M.D.
JUAN J. ARCE, M.D.
EZRA C. DAVIDSON, JR., M.D.

Divisions of Infectious Diseases and Perinatology, Departments of Internal Medicine and Obstetrics and Gynecology, Martin Luther King, Jr. General Hospital, Charles R. Drew Postgraduate Medical School, and University of Southern California School of Medicine, Los Angeles, California

INTRAPARTUM fetal monitoring is generally considered to be safe. However, the microbiologic safety of this procedure has not been evaluated. Cultures of amniotic fluid obtained through this catheter device at random revealed potentially pathogenic bacteria in 15 of the 30 women monitored during labor.[1] During this study, we encountered one case of gonococcal amnionitis later followed by neonatal sepsis.

A 14-year-old primipara was admitted on September 4, 1974, 3 hours after the rupture of membranes. Her last menstrual period was on November 11, 1973. During the first trimester, she was examined for sore throat when a routine sputum culture was positive for *Neisseria gonorrhoeae*. At term the blood pressure was 160/114 mm. Hg; pulse, 100 b.p.m.; respirations, 20 per minute; oral temperature, 98.6° F. There was pedal edema but no proteinuria. The uterus was 34 weeks' size, with 5 cm. cervical dilatation; the presenting part was at station zero. Routine urinalysis, blood cell counts, chest x-rays, and x-ray pelvimetry were unremarkable. The heart and lungs were clear. Laboratory data were as follows: glucose, 123 mg. per 100 ml.; blood urea, 4 mg. per 100 ml.; chloride, 105 mEq. per liter; bicarbonate, 22 mEq. per liter; sodium, 139 mEq. per liter; potassium, 3.3 mEq. per liter; lactic dehydrogenase, 214 mU. per milliliter; serum glutamic oxalacetic transaminase, 12 mU. per milliliter; alkaline phosphatase, 119 mU. per milliliter; total bilirubin, 1.0 mg. per 100 ml.; direct bilirubin, 0.2 mg. per 100 ml.; total protein, 6.5 Gm. per 100 ml.; albuminglobulin ratio, 3.6/2.9. The blood pressure was regulated by appropriate measures. The labor was monitored with an intrauterine catheter* and fetal scalp electrodes.† A live female child was delivered by forceps application 12 hours and 44 minutes after admission. During labor, cultures were obtained from the cervix and amniotic fluid was collected through the intrauterine catheter. The

Supported by Henry J. Kaiser Family Foundation Grant No. 1477-51224-XXX.

Reprint requests: Haragopal Thadepalli, M.D., Martin Luther King, Jr. General Hospital, 12021 S. Wilmington Ave., Los Angeles, California 90059.

*Transcervical intrauterine kit (B2069), Corometrics Medical Systems, Inc., Wallingford, Connecticut.

†Spiral electrode (B2462), Corometrics Medical Systems, Inc., Wallingford, Connecticut.

amniotic fluid was turbid. After delivery, umbilical cord blood was also cultured (see Table I).

The postpartum period was uneventful for 3 days; then she developed fever of 101° F. Pelvic examination at this time revealed foul smelling lochia when cultures of the cervix, blood, and the endometrium were obtained. She was then treated with ampicillin (500 mg.) administered by mouth four times a day. She became afebrile on the fifth day and was discharged on the seventh hospital day.

The infant weighed 3,450 grams (seventy-fifth percentile), the height was 54 cm. (ninetieth percentile), and the head circumference was 35 cm. (eightieth percentile). The general examination was normal. A superficial abrasion was noted on the scalp but findings were otherwise unremarkable. Newborn blood cultures were not obtained. The Apgar score at birth was 9/9 at 1 and 5 minutes. The child was asymptomatic for 3 days but then the temperature rose to 101° F. and she was transferred to the special-care nursery. A scab was seen at the site of the superficial scalp abrasion noted earlier, but showed no evidence of inflammation or pustule formation. Blood cultures were drawn and treatment was initiated with ampicillin (130 mg.) administered intravenously every 6 hours in addition to kanamycin (24 mg.) every 12 hours given intramuscularly, followed by prompt defervescence. The mother and daughter were discharged on the seventh hospital day.

Table I. Culture results

Cervix:	
	Neisseria (N) gonorrhoeae
	Enterobacter cloacae
	Staphylococcus epidermidis
	Diphtheroids
Blood (maternal):	
	No growth
Amniotic fluid:	
	Total count = 25/mm.^{3}
	N. gonorrhoeae
	Alpha streptococcus not group D
	Diphtheroids
Blood (neonatal—at birth):	
	Not done
Endometrium:	
	N. gonorrhoeae
Cord blood:	
	Staphylococcus epidermidis
	Diphtheroids
Blood (newborn—third day):	
	N. gonorrhoeae
Scalp wound:	
	Scab formed
	Not cultured

Maternal, cord, and neonatal blood was cultured in duplicate in tryptic soy broth (BBL) supplemented with sodium polyanetholesulfonate. All cultures were processed by aerobic and anaerobic bacteria. Aerobic bacteria were identified by conventional schema. Anaerobes were identified by their biochemical reactions in prereduced anaerobically sterilized media and gas-liquid chromatography patterns. *Neisseria gonorrhoeae* was identified by its growth on Thayer Martin media in candle-extinction jar, glucose fermentation, and positive oxidase reactions.

There are several pertinent features in this case. The mother was treated for pharyngeal gonorrhea during the first trimester. A past history of gonorrhoea perhaps should alert one to the possible onset of intrapartum gonococcal complications. Several modes of dissemination of gonococcus from the cervix could be postulated. A simple rupture of the membranes might itself be sufficient to cause amnionitis during labor. Prompt initiation of therapy in such instances was previously reported to avert neonatal sepsis.[2] Gonococcal scalp wound infections at the site where the electrode had been previously placed is another possible source (Morbidity & Mortality Weekly Report, p. 115, 1975, U. S. DHEW Pub. No. [CDC] 75-8017).

Gram stain of amniotic fluid failed to show gram-negative diplococci because they were in undetectably low concentration. Quantitative cultures of this fluid later revealed only 25 colonies of gonococci along with other bacteria per milliliter. It is of interest to note that maternal and cord blood cultures were negative for gonococci; therefore, the transplacental route appears unlikely. It was no surprise that the cervix and the endometrial samples were positive for *gonorrhoeae*. Either premature rupture of the membranes or the subsequent insertion of an intrauterine catheter or both might have caused amnionitis. Subsequent transmission of gonococcus to the newborn infant could have been either due to fetal ingestion of infected amniotic fluid or through inadvertent inoculation of gonococci into the fetal scalp by the electrodes inserted during fetal monitoring in the presence of contaminated amniotic fluid. In view of negative cord-blood cultures, transplacental transmission appears to be unlikely in this case. Modified Gram stain of the sections of the placenta, cord, and membranes revealed no bacteria.

In a prospective study of microbiology during labor conducted during the same period, about 110 pre- and postpartum cultures of the cervix were gram stained and cultured for both aerobic and anaerobic bacteria. None of the specimens, with the exception of this case, revealed gram-negative diplococci on Gram stain. Furthermore, none of the 110 cultures obtained in 55 women in the perinatal period showed any other gram-negative bacteria that could have been mistaken for gonococci, viz., veillonella, serratia, and acinetobacter. For this reason, we recommend that the cervical smears obtained during labor should be routinely Gram stained and inspected for gram-negative diplococci. Prompt therapy against gonococci should be initiated when gram-negative diplococci are seen. Such

October 15, 1976
Am. J. Obstet. Gynecol.

patients should not be routinely monitored during labor.

REFERENCES

1. Thadepalli, H., Appleman, M. D., Maidman, J. E., Chan, W. H., Arce, J. J., Hooper, D. G., Imagawa, D., and Davidson, E. C., Jr.: XV Intersci. Conf. Antimibcrob. Agents Chemother. 227, 1975.
2. Rothbard, M. J., Gregory, T., and Salerno, L. J.: AM. J. OBSTET. GYNECOL. **121:** 565, 1975.

Gonococcal salpingitis in pregnancy

RENE R. GENADRY, M.D.
BRUCE H. THOMPSON, M.D.
JENNIFER R. NIEBYL, M.D.

Department of Gynecology and Obstetrics, Johns Hopkins Hospital, Baltimore, Maryland

POSITIVE cervical cultures for gonorrhea have been reported with increasing frequency in pregnancy as well as in nonpregnant patients. Although pelvic inflammatory disease has occurred in pregnancy, it has usually been associated with septic abortion or has represented an exacerbation of pre-existing disease. Acute purulent salpingitis in pregnancy is rare, and we have been unable to find any previously reported case in which *Neisseria gonorrheae* was isolated from the Fallopian tubes during pregnancy. The patient reported here presented with acute abdominal pain simulating appendicitis, and had cultures positive for *N. gonorrheae* from acutely inflamed Fallopian tubes as well as from the cervix at 14 weeks of pregnancy.

A 21-year-old black woman, para 0, presented at 14 weeks of pregnancy with a history of lower abdominal pain of 24 hours' duration. She had some nausea and vomiting at the beginning of her pregnancy, but the nausea had increased during the preceding 24 hours and she vomited once on the morning of the admission. The pains were most marked in the right lower quadrant, with radiation to the left lower quadrant and right upper abdominal area. The remainder of her past history was unremarkable.

Her physical examination revealed: temperature, 100° F.; pulse 120 b.p.m.; respirations, 22 per minute; blood pressure, 160/90 mm. Hg. No bowel sounds were audible. The abdomen was diffusely tender with guarding in all four quadrants and rebound tenderness was present in both lower quadrants, more marked on the right. Pelvic examination disclosed a normal-appearing cervix which was soft and closed, with no bleeding, laceration, or unusual discharge. The uterus was enlarged compatible with a 14 week size pregnancy, and there was cervical motion tenderness bilaternally. The adnexa were tender but no masses were present.

Reprint requests: Jennifer R. Niebyl, M.D., Woman's Clinic 159, Johns Hopkins Hospital, Baltimore, Maryland 21205.

Laboratory data included: hematocrit, 37 per cent; white blood cell count, 18,700; urinalysis, normal; electrolytes, normal; serum urea nitrogen, 3; amylase, 69; total bilirubin, less than 0.8 mg. per deciliter. The chest x-ray was normal and the abdominal x-ray revealed a nonspecific gas pattern. The cervical smear showed gram-negative intracellular diplococci, and cervical culture subsequently confirmed the presence of *N. gonorrheae*.

Because of the presumptive diagnosis of acute appendicitis, an exploratory laparotomy was performed. At laparotomy, both tubes were hyperemic and congested. Purulent material dripped from the fimbriated ends, and free pus was present in the peritoneal cavity. The Gram stain of the purulent material showed gram-negative intracellular diplococci, and culture subsequently confirmed the presence of *N. gonorrheae* in the tubal exudate. The appendix was normal.

Postoperatively, the patient was treated with intravenous cephalothin, 4 Gm. per day, and kanamycin, 1 Gm. per day, for 5 days. She also received progesterone, 100 mg., intramuscularly every 6 hours for 24 hours, and 17-alpha-hydroxyprogesterone caproate, 250 mg., intramuscularly twice a week. She had a benign postoperative course and was discharged on the seventh hospital day. The remainder of her pregnancy was uncomplicated and at 37 weeks of gestation she went into labor spontaneously and delivered a normal 2,870 gram male infant. The placenta was normal and weighed 500 grams.

Before making the diagnosis of either acute salpingitis in pregnancy, or recurrent pelvic inflammatory disease associated with pregnancy, it is of utmost importance to assure that one is not dealing with a septic abortion. If there is any suggestive evidence, by either history or physical examination, of interference with the pregnancy, or suggestion of amnionitis, emptying of the uterus is mandatory.

Pre-existing pelvic inflammatory disease may undergo exacerbation during the course of an intrauterine pregnancy,[1] and a patient with no evidence of criminal interference may present with a previously unsuspected tubo-ovarian abscess. It is of note that many of these patients have an acute abdomen, often diagnosed preoperatively as appendicitis, twisted ovarian cyst, or ectopic pregnancy. However, the finding of *N. gonorrheae* on a cervical culture or gram stain does not necessarily explain the picture of acute abdominal pain, as this finding might well be coincidental and the patient have some other intra-abdominal pathology.

It has been classically taught that acute gonococcal salpingitis rarely if ever occurs in pregnancy, and several mechanisms have been invoked to explain this observation. The intact fetal membranes, the cervical mucus plug, the absence of menstruation and the decidua covering the openings to the uterine tubes have all been considered barriers to the ascent of infection.

Gonorrhea in the cervix can spread to the tubes via at least two separate routes: (1) by direct ascent through the endometrial cavity, or (2) via vascular channels. The introduction of infection may occur at

the same exposure as conception, thus explaining acute gonococcal salpingitis associated with very early pregnancy. Also, one postulated barrier to ascent of infection, the obliteration of the endometrial cavity by the pregnancy, is not complete until the end of the first trimester, when the fusion of the decidua capsularis and the decidua parietalis occurs.[2] Thus, the gonococcus may ascend directly via the endometrial cavity, without direct interference with the pregnancy, until about 15 weeks from the patient's last menstrual period.

Bacteria may also ascend by lymphatic extension into the parametra, or produce a bacteremia, as evidenced by the association of gonococcal arthritis with pregnancy. This mechanism must also explain acute salpingitis occurring later in pregnancy. It is possible that cases of septic abortion in which patients deny interference with the pregnancy actually are caused by gonococcal infections leading to infected abortions.

In previously reported cases of acute salpingitis in pregnancy, the gonococcus had never been recovered from the tubes. Other organisms isolated in these cases may have been secondary invaders in situations in which gonorrhea was not detected because of the fastidiousness of the organism, or because of the lack of currently available culture techniques. Nevertheless, the case reported here confirms the coexistence of acute gonococcal salpingitis and a 14 week intrauterine pregnancy which subsequently carried to term.

REFERENCES

1. Acosta, A. A., Mabray, C. R., and Kaufman, R. H.: Intrauterine pregnancy and coexistent pelvic inflammatory disease, Obstet. Gynecol. **37:** 282, 1971.
2. Hamilton, W. J., and Boyd, J. D.: Development of the human placenta, *in* Phillip, E. E., Barnes, J., and Newton, M., editors: Scientific Foundations of Obstetrics and Gynecology, Philadelphia, 1970, F. A. Davis Company, p. 204

Hydatidiform mole and eclampsia with coexistent living fetus in the second trimester of pregnancy

BERNARD J. SICURANZA, M.D.
LESLIE HUGHES TISDALL, M.D.

Department of Obstetrics and Gynecology, St. Mary's Hospital Division, Catholic Medical Center of Brooklyn and Queens, New York

ECLAMPSIA occurring in the presence of hydatidiform mole is not too uncommon. We have been unable to find a case of this combination existing with a living fetus.[1, 2] Accordingly, we felt the following case was worthy of reporting.

Reprint requests: Dr. Bernard J. Sicuranza, Department of Obstetrics and Gynecology, St. Mary's Hospital Division, Catholic Medical Center of Brooklyn and Queens, Brooklyn, New York 11213.

A 16-year-old black girl, gravida 1-0-0-0, whose last menstrual period occurred on October 3, 1973, was admitted on February 6, 1974 with complaints of generalized convulsions, severe headache, and vomiting for 2 days prior to admission. The patient gave a history of recent vaginal bleeding for which she was seen in the emergency room of another hospital and referred to the gynecologic clinic.

There was no history of hypertension, epilepsy, headaches, epigastric pain, or visual disturbance.

On admission, the patient was anxious and excitable but was in no acute distress. The pulse rate was 100 per minute, respirations 24 per minute, and the blood pressure 160/100 mm. Hg. A general physical examination was within normal limits. The uterus was 20 to 22 weeks in size, somewhat larger than the reported period of gestation. The fetal heart was audible by Doptone. No other organomegaly was noted. The extremities revealed no edema; hyperreflexia was marked. The eye grounds showed a ratio of 3:1 with marked nicking.

Two urinary chorionic gonadotropin tests were positive in titers of 1-2048 and 1-1716. The urinalysis revealed 4+ albumin and numerous granular casts. The lactic dehydrogenase was 301; serum glutamic oxalacetic transaminase, 148; serum glutamic pyruvic transaminase, 47. The hemoglobin electrophoresis was A 49.2, S.45.4 A_2 4.7. The chest x-ray revealed that the heart was slightly enlarged. An abdominal x-ray showed that the uterus was 20 weeks in size with a single fetus. A diagnosis of molar pregnancy with eclampsia and coexistent fetus was made.

Treatment was initated with morphine and magnesium sulfate. On February 5, 1974, a hysterotomy was done with the delivery of a living male fetus, weighing 125 grams, who died shortly after birth. The patient had one more convulsion 4 hours after hysterotomy which was controlled with morphine and magnesium sulfate. She improved steadily and was discharged 10 days later with a urinary chorionic gonadotropin still positive. This gradually cleared by day 40 post partum. Serum gonadotropins were negative by the third month post partum. The pathologic report stated that the maternal surface of the placenta showed large chorionic villi with marked myxomatous changes. The diagnosis was hydatidiform mole.

This patient was 16 years old. We have recently treated two other patients who had mole with a living fetus, but without eclampsia—one 16 years of age and the other 24. In Beischer's[1] series the average age was 24. He also reported hemorrhage in about 50 per cent of the cases. Our patient had minimal bleeding. The two other patients we managed had no bleeding.

Onset of toxemia before week 28 of gestation has been the most consistent reliable diagnostic sign in these cases. While eclampsia was present in only one of Beischer's[1] 92 cases of fetus with coexistent mole, 21 of these had fulminating toxemia. The presence of a fetus is erroneously considered by some to rule out hydatidiform mole. The finding of a single fetus is helpful since it excluded multiple gestation as a cause of early toxemia and eclampsia. The male: female ratio

as reported is 1:3. The fetus in this case was male; the other two fetuses were female. This fetus was born alive but died shortly thereafter; our other two fetuses were stillborn. Beischer reported 54 stillborn and 38 live births with 19 survivors. Ultrasound was not used in our case as the convulsive state necessitated speedy resolution; however, it was disappointing in our other cases. One was reported as negative, and the other was inconclusive until the presence of a fetus was confirmed by amniography. Ultrasound might be expected to help make the diagnosis but the molar transformation would have to be extensive for this to be made. With a coexistent fetus the molar transformation may be only minimal.[1]

A urinary chorionic gonadotropin level of 350,000 I.U. per liter, or a serum level of more than 320 I.U. per milliliter, after day 100, has been found to be consistently accurate in diagnosing the presence of a mole. Our patient had a titer of at least 3,000,000 I.U. per liter of urine. Titers of greater than 350,000 I. U. per liter of urine were also present in our other two cases. It would seem, then, that in any case of toxemia with an early onset a titer of urinary chorionic gonadotropins should be done. It is an inexpensive and rapid test and would undoubtedly uncover many cases without extensive molar transformation which might be missed at delivery.

REFERENCES

1. Beischer, N. A.: Aust. N. Z. J. Obstet. Gynaecol. **6:** 127, 1966.
2. Jones, W. B., and Lauersen, M.D.: Am. J. Obstet. Gynecol. **122:** 267, 1975.

Iatrogenic intravesical foreign body following Marshall-Marchetti procedure

JAN C. SESKI, M.D.

Department of Obstetrics and Gynecology, University of Michigan Medical Center, Ann Arbor, Michigan

A variety of surgical procedures have been developed over the years for the correction of stress incontinence in the female patient. Some of these have involved, in one form or another, a retropubic cystourethropexy as described by Marshall, Marchetti, and Krantz.[2] Although modifications of the original Marshall-Marchetti-Krantz operation have been proposed, the basis for its success rests upon an elevation and suture fixation of the vesical neck to a retropubic position. Various suture materials have been used to suspend the urethra and vesical neck to the symphysis pubis, Cooper's ligament, or rectus abdominis fascia. The suture materials used are either absorbable, as was described in the original Marshall-Marchetti-Krantz procedure, or nonabsorbable, as is suggested by some surgeons.

Reprint requests: Jan C. Seski, M.D., Department of Obstetrics and Gynecology, University of Michigan Medical Center, Ann Arbor, Michigan 48104.

Three representative cases of iatrogenic intravesical foreign body in the form of nonabsorbable suture following Marshall-Marchetti-Krantz procedure are presented. The diagnosis and treatment of this avoidable complication are discussed.

C. C. was a 54-year-old white woman with a history of recurrent urinary tract infections and symptoms of stress incontinence. Two years previously, she underwent a Marshall-Marchetti-Krantz procedure employing silk sutures. Upon admission to the Medical Center, her urine was infected. An excretory urogram disclosed the presence of a 2 mm. intravesical calcification, and cystometry revealed a previously undiagnosed uninhibited neruogenic bladder. Cystoscopic examination found two stone-encrusted loops of silk protruding through the bladder mucosa, and these were removed transurethrally with a biopsy forceps.

Following this, the patient did well on a program of anticholinergic medications and a frequent voiding program. Her urge incontinence and recurrent urinary tract infections resolved.

N. C. was a 52-year-old black woman with a long history of repeated urinary tract infections which had increased in frequency since a Marshall-Marchetti-Krantz procedure was performed with nonabsorbable sutures. Her excretory urogram was normal, but cystometry showed a large capacity bladder. At the time of cystoscopy, a Dacron suture in the superior aspect of the urinary bladder was noted and removed transurethrally with a biopsy forceps.

On a program of frequent voiding, the patient has had no further urinary tract infections. Oral ephedrine sulfate had relieved her mild stress incontinence.

K. L., a 44-year-old white woman, underwent total abdominal hysterectomy and a Marshall-Marchetti-Krantz procedure; nonabsorbable sutures were employed in the suspension. Two months later, she complained of persistent frequency, dysuria, urge incontinence, and pyuria. Her excretory urogram was unremarkable. Cystoscopic examination found multiple Tevdek (Deknatel Corp.) sutures in the bladder lumen surrounded by marked inflammatory response and bullous edema. The sutures were removed transurethrally with biopsy forceps.

Since removal of the sutures, the patient's symptoms of urgency and urge incontinence have disappeared and her urine has remained sterile.

The cases presented illustrate the hazards involved when permanent suture materials are employed in the Marshall-Marchetti-Krantz procedure. The high incidence of hematuria following this operation suggests that, more often than not, sutures are unknowingly passed through the bladder mucosa.

Lapides[1] has recommended that the suspension be accomplished by taking 1 cm. "bites" with absorbable chromic suture through the bladder wall in order that the sutures do not pull through prematurely. If absorbable sutures are used and entry into the bladder occurs, it will be of no consequence, provided that the intramural portion of the ureter is not compromised.

Persistent irritative bladder symptoms, hematuria,

pyuria, and intravesical calculi following a Marshall-Marchetti-Krantz procedure are highly suggestive of inadvertent placement of permanent sutures into the lumen of the bladder. Cystoscopy will be diagnostic if the cause is the presence of intravesical sutures. These should be resected transurethrally, for attempts at treating irritative bladder symptoms with antispasmodics and urinary antibiotics will be ineffectual until the foreign bodies are removed.

Some authors suggest that permanent sutures might be acceptable in a suspension when a transvesical or open-bladder approach is used, in which case, placement of a suture through the bladder mucosa could be immediately recognized and corrected. However, with permanent suture, one still risks potential morbidity from chronic osteitis pubis, which is the most common major complication occurring after bladder suspension with the Marshall-Marchetti-Krantz procedure.

Permanent suture does not make a suspension more permanent. The basis for the strength of the urethrovesical suspension lies in the scarring and fixation of the paraurethral fascia to the retropubis. Absorbable sutures simply maintain the new anatomic position of the vesical neck until the patient's own fibrous tissue formation occurs and takes over for the sutures.[1]

The complications following the use of permanent suture for the Marshall-Marchetti-Krantz procedure far outweigh any potential advantages. Therefore, the use of nonabsorbable suture cannot be justified.

REFERENCES

1. Lapides, J.: Operative technique for stress urinary incontinence, Urology **3**: 657, 1974.
2. Marshall, V. F., Marchetti, A. A., and Krantz, K. E.: The correction of stress incontinence by simple vesicourethral suspension, Surg. Gynecol. Obstet. **88**: 509, 1949.

Amylase-containing ovarian cystadenocarcinoma simulating a pancreatic pseudocyst

R. R. JOSEPH, M.D.
C. F. FREY, M.D.
R. MICHAELS, PH.D.
D. S. MCCANN, PH.D.

Departments of Internal Medicine and Surgery, Wayne County General Hospital, Eloise, Michigan, and The University of Michigan Medical School, Ann Arbor, Michigan

SALIVARY glands and pancreas are the conventionally accepted sources of amylase. While there is evidence implicating liver as an α-amylase–synthesizing organ,[1] this has been proved definitively only for the rat. In human subjects, Fallopian tubes have been shown to contain the enzyme and high serum amylase levels are sometimes associated with Fallopian tube pathology.[2] It is not widely appreciated that human ovaries also may contain amylase. We recently encountered a patient with cystadenocarcinoma of the ovary containing fluid with extremely high amylase levels.

A 77-year-old white woman was referred to us for treatment of intractable ascites. She had noted a marked increase in abdominal girth over the last 2 years, but denied all other symptoms. Her past history was essentially unremarkable.

On physical examination, the abdomen was extremely protuberant with a prominent venous pattern radiating from the midline. Shifting dullness was noted throughout the abdomen with a positive fluid wave. Pelvic examination showed a freely movable uterus with apparently clear adnexal areas. The ovaries were not palpated.

Initial laboratory findings included: white blood count, 11,600 per cubic millimeter; hemoglobin, 13.0 Gm. per 100 ml.; hematocrit, 39.1 per cent; blood urea nitrogen, 25 mg. per 100 ml.; fasting blood sugar, 115 mg. per 100 ml.; sodium, 141 mEq. per liter; potassium, 4.1 mEq. per liter; calcium, 8.4 mg. per 100 ml.; phosphorus, 5.5 mg. per 100 ml.; serum glutamine pyruvic transaminase, 15 U. per milliliter; lactic dehydrogenase, 160 U. per milliliter; bilirubin, 0.7 mg. per 100 ml.; albumin, 4.4 Gm. per 100 ml.; globulin, 2.2 Gm. per 100 ml.; prothrombin time, 100 per cent; serum amylase, 56 U. per milliliter (Somoygi units) (normal, 40 to 120 U.); serum lipase, 0.8 U. per milliliter.

Diagnostic paracentesis yielded 50 c.c. of cloudy, brownish fluid. Cytologic examination for malignant cells was negative. Specific gravity, 1.081; protein, 12.8 Gm. per 100 ml.; albumin, 7.92 Gm. per 100 ml.; alpha, beta, and gamma globulins, 1.76, 1.71, and 1.38 Gm. per 100 ml.; calcium, 11.5 mg. per 100 ml.; phosphorus, 0.5 mg. per 100 ml.; lactic dehydrogenase, 280 U. per milliliter; amylase, 7,050 U. per milliliter.

A technetium-99 liver-spleen scan was interpreted as abnormal, with diffuse hepatocellular disease and splenomegaly. An ultrasonic echogram of the abdomen showed a large, fluid-filled cavity, with displacement of most of the gas-filled bowel to the upper abdomen, leading to an impression of a massive intra-abdominal fluid collection, probably ascites. Selective splenic and pelvic arteriography showed upward stretching and displacement of the distal branches of the superior mesenteric artery suggestive of an ovarian or mesenteric cyst. Upper gastrointestinal series and small bowel follow-through showed a normal esophagus and duodenum, but displacement of the entire small bowel into the upper abdomen. Intravenous pyelogram showed a large amount of abdominal fluid, minimally dilated ureters, and extensive compression of the left lateral superior portion of the bladder.

Exploratory laparotomy was performed. Almost immediately upon entering the peritoneal cavity, a massive ovarian cyst was encountered. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. The right ovarian cystic mass was a well-differentiated papillary serous cystadenocarcinoma.

The high amylase activity in the ovarian cyst fluid suggested that ovaries might inherently contain the

This research was supported in part by the Medical Staff Research and Education Fund of Wayne County General Hospital, Eloise, Michigan.

Reprint requests: Dr. R. R. Joseph, Department of Medicine, Wayne County General Hospital, P.O. Box 124, Eloise, Michigan 48132.

enzyme. Consequently the amylase from the cyst fluid, concentrated and partially purified by gel chromatography, was compared by disc gel electrophoresis with amylase extracted, purified, and concentrated from an ovary excised from a patient with pelvic inflammatory disease.

Alpha-amylase activity of the initial ovarian homogenate was 9.2 U.* for 107 mg. of protein, well in excess of any value attributable to residual blood. After partial purification and concentration, a specific activity of 5.05 U.* per milligram of protein was attained. The ovarian cyst fluid from the patient, similarly purified and concentrated, yielded an α-amylase fraction with a specific activity of 128 U.* per milligram of protein.

No increase in reducing groups was observed when the two purified preparations were incubated with maltose, confirming that the observed hydrolytic activity was that of an α-amylase.

Disc gel electrophoresis, pH 8.8, demonstrated three isoenzymes. A single band with $R_f = 0.03$, presumably corresponding to one isoamylase, was obtained for the ovarian cyst preparation; the ovary yielded two isoamylases, a major component of $R_f = 0.26$ and a minor component with $R_f = 0.09$. The difference in isoenzyme composition between the two preparations was ascribed to the fact that they were obtained from two different individuals with unrelated diseases, one of which involved a neoplasm.

A recent study[2] suggested that elevated serum amylase levels might be used to differentiate Fallopian tube from ovarian lesions. Our studies indicate that human ovaries probably also produce amylase. Thus, an elevated amylase level in serum, cyst fluid, or peritoneal fluid cannot exclude the ovary as the site of abnormality.

*One unit of amylase activity was defined as the production of 1 μM of maltose reducing equivalents per minute from soluble starch at 37° C. at pH 7.0.

Thanks are due to Mr. Gary Foster for his excellent technical assistance.

REFERENCES

1. Joseph, R. R., Olivero, E., and Ressler, N.: Electrophoretic study of human isoamylases, Gastroenterology **51:** 377, 1966.
2. Hochberg, C. J.: Tubal amylase, Obstet. Gynecol. **43:** 129, 1974.

CORRESPONDENCE

Siblings with gonadal dysgenesis

To the Editors:

Drs. Fleishman, Berlin, and Dana, in their report on siblings with gonadal dysgenesis (AM. J. OBSTET. GYNECOL. 124: 208, 1976), lament the often-seen poor management of the patient with this problem, yet they themselves are guilty of that which they ascribe to others. The evaluation of their patients was quite thorough through the claim that mosaicism was not present is not valid insofar as only one cell line was evaluated.

However, I must take exception to their method of management. To subject a young woman with proved gonadal dysgenesis to laparotomy, remove the gonads, and leave the uterus behind are inconsistent with the policy dictated by current knowledge.

Long before the recent suggested association between conjugated estrogens and endometrial carcinoma,[1] the malignant potential of the endometrium in the presence of a dysgenetic gonad was recognized.[2]

I submit that the gynecologists involved here would not, under other circumstances, have removed benign gonads and left a useless uterus behind (the one exception being ablative therapy for carcinoma of the breast).

I do not envy the physicians or the patients involved here who must now be concerned that every instance of irregular bleeding represents endometrial carcinoma.

I would suggest that strong consideration be given to removing the uterus from these two young women and, further, that for any patients with a proved diagnosis of gonadal dysgenesis—regardless of whether a Y chromosome is present or not—appropriate therapy consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy and nothing less.

Michael D. Birnbaum, M.D., F.A.C.O.G.
Department of Reproductive Endocrinology
Division of Gynecology-Obstetrics
Albert Einstein Medical Center
Philadelphia, Pennsylvania 19141

REFERENCES

1. Smith, D. C., Prentice, R., Thompson, D. J., et al.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. **293:** 1164, 1975.
2. Cutler, B. S., Forbes, A. P., Ingersoll, F. M., et al.: Endometrial carcinoma after stilbestrol therapy in gonadal dysgenesis, N. Engl. J. Med. **287:** 628, 1972.

Reply to Dr. Birnbaum

To the Editors:

Dr. Birnbaum makes several points in his letter. The first is that mosaicism was not ruled out since only one cell line was evaluated. This is true but inconsequential since the presence of the X-Y line determines the subsequent therapy.

The second statement, that in a young woman with gonadal dysgenesis, to remove the gonads and leave the uterus behind ". . .are inconsistent with the policy dictated by current knowledge" is a rather strong, blanket statement that one might expect from someone inexperienced in dealing with the "whole" patient. We will go into this further.

The malignant potential of the endometrium under continuous estrogen stimulation alone and that this has been well known, even to laymen, for a long period of time are facts that no one would argue. These patients are on cyclic progestogens. A particular potentiality for endometrial carcinoma in patients with dysgenetic gonads left untreated is nowhere in the literature; in fact, it is quite the contrary: The principle of prophylactic removal of potentially malignant organs would hardly be a reasonable approach on the basis of potentiality only. The degree of risk is what must be weighed against the potential benefits.

The first article quoted, by Smith and associates, shows an association between exogenous estrogen therapy and an increased risk of endometrial carcinoma. Nowhere in the article is the conclusion reached that prophylactic hysterectomies be performed.

The second article, by Cutler and colleagues, should again show the possible association of exogenous estrogen with endometrial carcinoma. The authors conclude that "close supervision" is advisable but nowhere do they suggest hysterectomy.

To return to the point alluded to earlier, we would suggest that the sophoromic author of the critical letter ponder the possible results of hysterectomy in two young women, one a teen-ager, who already doubt their sexual identity. We might further suggest his reviewing the literature regarding the psychological aspects of hysterectomy in women of all ages. We would further ask him to ponder the possibility of pregnancy via implantation, at a future date, if such a procedure became available.

We cannot believe that Dr. Birnbaum is seriously

suggesting a second operation for removal of the uterus in these two patients, who are both aware of the necessity for close supervision.

His final dogmatic statement reminds us of a correct diagnosis made by a medical student and missed by all the attending and house physicians. When asked how he arrived at the correct diagnosis of pancreatitis, he said, "Left upper quadrant pain, what else could it be!"

Melvin Berlin, M.D., F.A.C.O.G.
Milton M. Dana, M.D., F.C.A.P.
Philip Fleishman, M.D., D.-I.M.
South Shore Surgical-Gynecological-Obstetrical Group, P.C.
Islip Terrace Professional Building
111 Carleton Avenue
Islip Terrace, Long Island, New York 11752

Immunologic aspects of term pregnancy toxemia

To the Editors:

I was very much interested in the article by Drs. Yang and associates, "Immunologic aspects of term pregnancy toxemia" (AM. J. OBSTET. GYNECOL. 122: 727, 1975).

I would like to ask the authors whether they had occasion to examine the umbilical cords of these children. When the cord shows lesions of necrotic funiculitis, also called subacute funiculitis, an increase in immunoglobulin M, up to 1 to 2 Gm., is frequently observed, although no infection—bacterial, viral, or parasitic—can be demonstrated. These children are apt to have marked leukocytosis (up to 50,000 white cells); they show no clinical sign of infection, and, when they die (many of them are premature), no visceral, acute, or cicatricial lesion is found to suggest a recent or old infection. At any rate, the children treated with antibiotics are being given the biological elements.

For some years I have been wondering whether such a picture does not correspond to a state of noninfectious immunity, but I am unable to clarify this problem from the anatomic standpoint.

S. Sarrut, M.D.
Institut de Puericulture
Centre Neo-Natal (Pr. Salge)
26, Blvd. Brune
75014 Paris, France

Reply to Dr. Sarrut

To the Editors:

I appreciate the interest in my article. In order to answer the question raised in the letter, I again reviewed our data. In our study, as stated clearly in the article, we carefully excluded any case with possible infection, during either the gestation period or labor, since this would have interfered with the whole purpose of our study. We observed 2 stillborn infants among the toxemia group, but we could only obtain cord blood from one; the immunoglobulin M level was 12 mg. per cent. The other stillborn infant was macerated; therefore, no cord blood could be obtained. The highest immunoglobulin M level among the babies born to mothers in the toxemia group was 83 mg. per cent. We did not observe any newborn infant with lesions of necrotizing funiculitis and a highly elevated immunoglobulin M concentration.

Sen-Lian Yang, M.D.
The University of Chicago
Department of Obstetrics and Gynecology
The Chicago Lying-in Hospital
5841 Maryland Avenue
Chicago, Illinois 60637

Pituitary responsiveness to luteinizing hormone–releasing hormone (LH-RH) during pregnancy and the postpartum period

To the Editors:

I read with great interest the article, "Pituitary responses to LRH in the postpartum periods," by Friedman and his associates.[1] In this article, Dr. Friedman and his associates reported that no statistically significant changes in the levels of serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) could be demonstrated in five subjects on postpartum Day 1 or 3 and in the three subjects on postpartum Day 8 following a subcutaneous injection of 100 μg of synthetic LH-RH, and a normal elevation of LH and FSH following LH-RH injection was demonstrated in only one subject 36 days post partum.

In our laboratory, pituitary responsiveness to LH-RH during pregnancy and the postpartum period was previously investigated, and the results were reported elsewhere.[2, 3] Synthetic LH-RH was administered intravenously in a dose of 200 μg to 14 normal pregnant women and 20 normal lactating women. Serum FSH was detectable but relatively low in all 14 subjects in the first, second, and third trimesters of pregnancy. Moreover, exogenously administered synthetic LH-RH failed to stimulate serum FSH secretion from the anterior pituitary, and there was no rise in serum FSH in all 14 subjects throughout pregnancy. Synthetic LH-RH also failed to evoke FSH secretion in eight volunteers in the first postpartum week. About half of the six subjects in the third postpartum week responded to synthetic LH-RH with a rise of serum FSH and LH. All six lactating women in the fifth postpartum week were responsive to LH-RH, and there was a concomitant release in serum FSH and LH.

The findings reported by Dr. Friedman and his associates are in agreement with the results of our previous reports demonstrating a persistence of pitu-

itary suppression during pregnancy and the early postpartum period. Thus, it might be concluded that gonadotropic activity of the adenohypophysis is suppressed by an unknown mechanism throughout pregnancy and the early postpartum period. Further studies to elucidate the mechanism of suppression are needed.

Ryosuke Nakano, M.D.

Associate Professor
Department of Obstetrics and Gynecology
Kobe University
School of Medicine
Kobe, Japan

REFERENCES

1. Friedman, C., Gaeke, M. E., Fang, V., and Kim, M. H.: AM. J. OBSTET. GYNECOL. **124:** 75, 1976.
2. Nakano, R., Kayashima, F., Katayama, K., Mizuno, T., Washio, M., and Tojo, S.: Acta Obstet. Gynecol. Scand. **53:** 259, 1974.
3. Nakano, R., Kayashima, F., Mori, A., Kotsuji, F., Hashiba, N., and Tojo, S.: Acta Obstet. Gynecol. Scand. **53:** 303, 1974.

BOOKS

Books received

Atlas of Ultrasonic Diagnosis in Obstetrics and Gynecology. Karl-Heinz Schlensker. 158 pages, illustrated. Acton, Massachusetts, 1975, Thieme-Edition/Publishing Sciences Group, Inc. $32.00.

Child in Sport and Physical Activity. International Series on Sport Sciences. Vol. 3. Edited by J. G. Albinson and G. M. Andrew. 233 pages. Baltimore, 1976, University Park Press. $16.50.

Human Behavior and the Helping Professions. Otto Pollak. 98 pages. New York, 1976, Halsted Press, A Division of John Wiley & Sons, Inc. $7.95.

Obesity: Etiology, Treatment and Management. Edited by Milton V. Kline, Lester L. Coleman, and Erika E. Wick. 450 pages. Springfield, Illinois, 1976, Charles C Thomas, Publisher. (Price not available.)

Proceedings from the Symposia of the Fifth Congress of the International Primatological Society. (Nagoya, Japan. August, 1974.) Edited by S. Kondo, M. Kawai, A. Ehara, and S. Kawamura. 591 pages, illustrated. Tokyo, Japan, 1975, Japan Science Press. $60.00.

Recent Advances in Human Reproduction. (Proceedings of the First International Congress on Human Reproduction, Rio de Janeiro, Brazil, November 11-14, 1974.) Edited by A. Campos da Paz, V. A. Drill, M. Hayashi, W. Rodrigues, and A. V. Schally. 335 pages, illustrated. New York, 1976, Excerpta Medica Foundation. $46.95 soft cover.

Reviews in Perinatal Medicine. Vol. I. Edited by Emile M. Scarpelli and Ermelando V. Cosmi. 396 pages, illustrated. Baltimore, 1976, University Park Press. $24.50.

Season of Birth: A Study of Schizophrenia and Other Mental Disorders. Per Dalén. 166 pages. New York, 1975, North-Holland Publishing Company. $13.50 soft cover.

The Chromosome Disorders. Third edition. G. H. Valentine. 184 pages, illustrated. Philadelphia, 1976, J. B. Lippincott Company. $15.00.

The Management of Labour. Proceedings of the Third Study Group of the Royal College of Obstetricians and Gynaecologists, 1975. Edited by Richard Beard, Michael Brudenell, Peter Dunn, and Denys Fairweather. 276 pages, illustrated. London, 1976, The Royal College of Obstetricians and Gynaecologists. (Price not available.)

INDEX TO ADVERTISERS

Abbott Laboratories
Iberet-500/Iberet-Folic-500 ---------- 42, 43

Ayerst Laboratories
Premarin ---------- 20, 21, 22

B-D Electrodyne
Fetal Monitors ---------- 2, 3

Baylor College of Medicine
Postgraduate Course ---------- 8

Carnrick Laboratories
Hormonin ---------- 6

Corometrics Medical Systems, Inc.
Fetal Monitor ---------- 29

Flint Laboratories
Synthroid ---------- 50, 51, 52

Frigitronics of Connecticut Inc.
Frigi Colposcope ---------- 53

Hamot Medical Center
Classified ---------- 43

Holland-Rantos Co., Inc.
Korostatin ---------- 54

MDT Corporation
Chemiclave and Vibraclean ---------- 4

Mead Johnson Laboratories
Estrace ---------- 14, 15, 16
Peri-Colace ---------- Fourth Cover

Ortho Pharmaceutical Corporation
Monistat ---------- 32, 33
Ortho-Novum 1/50 ---------- 55, 56
Ortho-Novum 1/80 ---------- 47, 48
Sultrin ---------- 24, 25

Parke, Davis & Company
Tabron ---------- 39

Picker Corporation
Echoview System 80L ---------- 36, 37

Purdue Frederick Company, The
Senokot S ---------- 12

Roche Laboratories
Azo Gantanol ---------- 30, 31

St. Luke's Hospital
Classified ---------- 35

Searle & Co., G.D.
Cu-7 ---------- Second Cover, 1
Flagyl ---------- 58, Third Cover

Smith Kline & French Laboratories
Ancef ---------- 44, 45, 46

Sonicaid, Inc.
Fetal Heart Detectors ---------- 10

Storz Endoscopy, Karl-America, Inc.
Laparoscopes ---------- 40, 41

University of Michigan
Classified ---------- 18

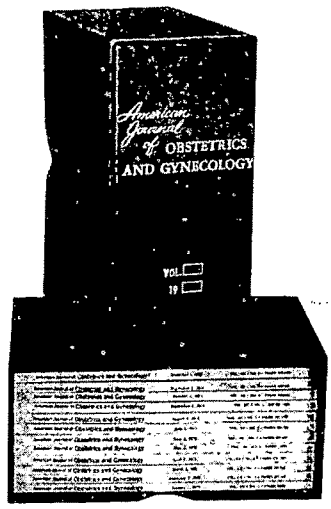
University of Tennessee
Classified ---------- 10

Welch Allyn, Inc.
Disposable Vaginal Specula ---------- 38

West Virginia University
Classified ---------- 43

Wyeth Laboratories
Lo/Ovral ---------- 26, 27, 28
Ovral ---------- 49

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼" × 11") for 1975 copies
☐ OLD SIZE (7¼" × 10½") for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

Flagyl®

(metronidazole) 250 mg.

Warning

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

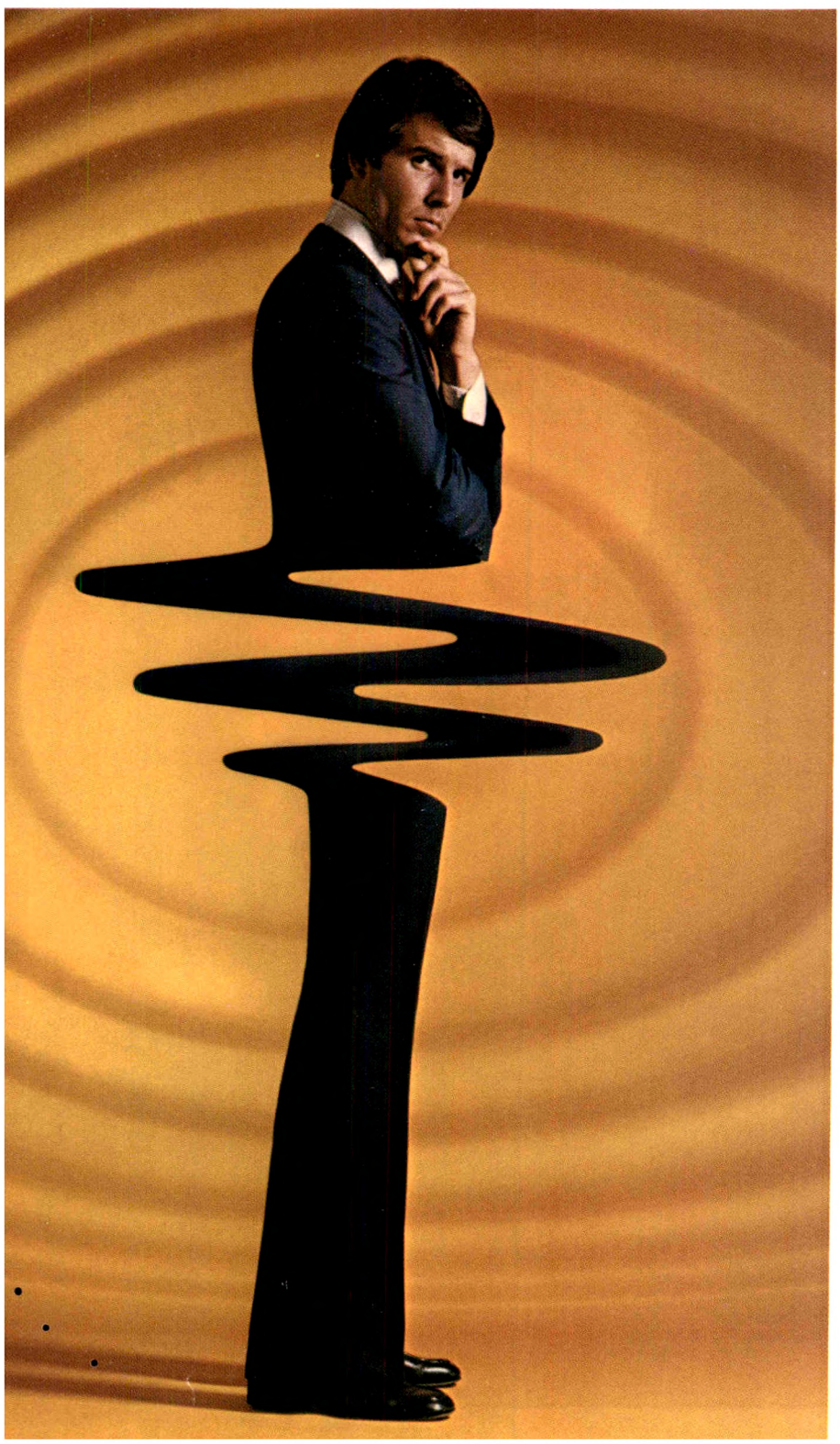
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

SEARLE Searle & Co.
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co.
Medical Department, Box 5110, Chicago, Ill. 60680

If men suffered from the symptoms of trichomoniasis, they'd appreciate Flagyl®.

(metronidazole)



Women with trichomoniasis have been grateful for the benefits of Flagyl therapy for over a decade. Most men have no symptoms and are not even aware that they have contracted trichomoniasis, so they rarely appreciate Flagyl. Unless both sexual partners are diagnosed and treated simultaneously, reinfection from the consort is a probability (the "ping-pong" effect).

In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra and the bladder. Only the systemic action of Flagyl can eliminate trichomonads from these sequestered sites.

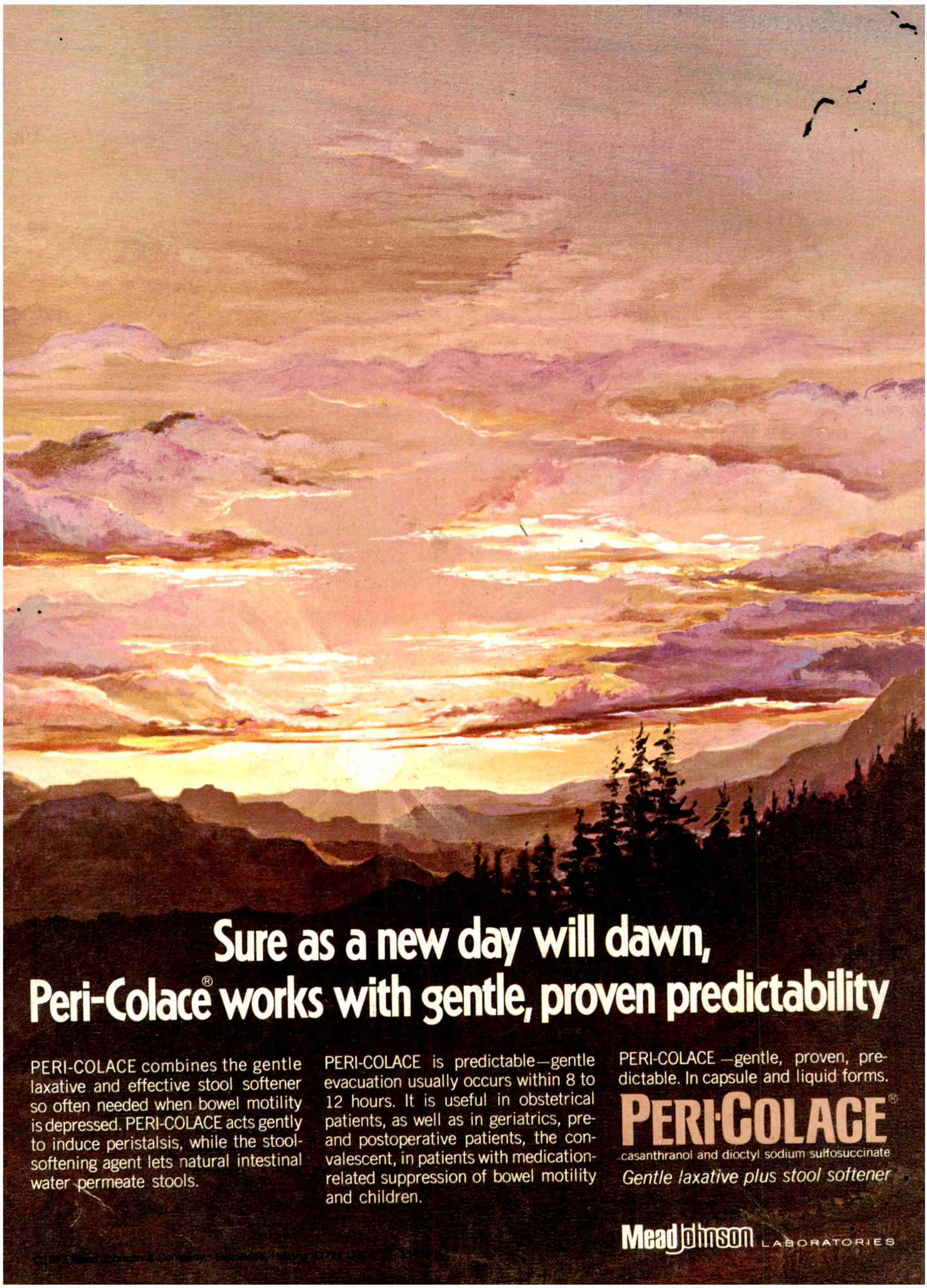
In the male, only Flagyl can effectively eliminate trichomonads from the male genitourinary tract.

Thus, for the female Flagyl is the treatment of choice. For the male it is the only choice. And that's something they both can appreciate!

Flagyl®
(metronidazole)
250-mg. tablets

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Please see adjacent page for brief summary of prescribing information.



Sure as a new day will dawn, Peri-Colace® works with gentle, proven predictability

PERI-COLACE combines the gentle laxative and effective stool softener so often needed when bowel motility is depressed. PERI-COLACE acts gently to induce peristalsis, while the stool-softening agent lets natural intestinal water permeate stools.

PERI-COLACE is predictable—gentle evacuation usually occurs within 8 to 12 hours. It is useful in obstetrical patients, as well as in geriatrics, pre- and postoperative patients, the convalescent, in patients with medication-related suppression of bowel motility and children.

PERI-COLACE—gentle, proven, predictable. In capsule and liquid forms.

PERI-COLACE®

casanthranol and dioctyl sodium sulfosuccinate

Gentle laxative plus stool softener

Mead Johnson LABORATORIES

©1973 Mead Johnson & Company

24.3.77

November 1, 1976
volume 126, *number* 5

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

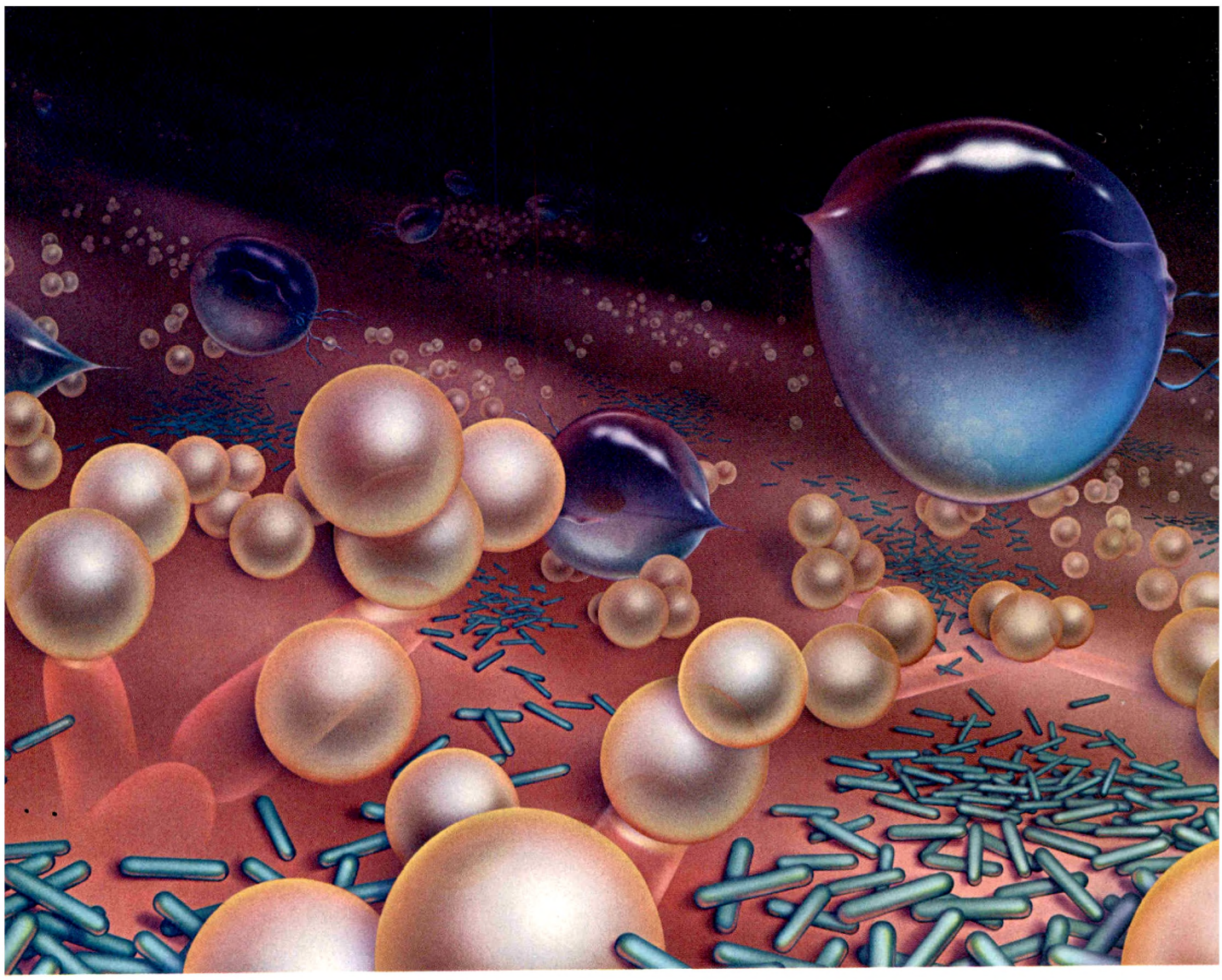
Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

Official Publication
AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY



Published by
THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (5) 521-626 (1976)



VAGINITIS*

VAGITROL®

CREAM
(sulfanilamide 15.0%, allantoin 2.0%, aminiacrine hydrochloride 0.2%)

SUPPOSITORIES
(sulfanilamide 1.05 g, allantoin 0.14 g, aminacrine hydrochloride 0.014 g)

Usually uncomfortable and embarrassing, your patient wants fast relief.

Prompt symptomatic relief† of itching, burning, discharge, malodor...

Often more than one pathogen is involved.

...when the specific organism is unknown.

*This drug has been evaluated as probably effective for this indication. See brief summary.

See following page for summary of prescribing information.

NOTE:
If possible, base treatment on specific diagnoses from sound clinical and laboratory methods.

INDICATIONS

Based on review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

†"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually Trichomonas vaginalis, Candida albicans, or Haemophilus vaginalis) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to Haemophilus vaginalis or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS

Hypersensitivity to product ingredients or sulfonamides. Kidney disease.

WARNINGS

Pregnancy: Safe use not established. Teratogenic potential of sulfonamides not thoroughly investigated. However, a significant increase in the incidence of cleft palate and other body abnormalities of offspring was observed when sulfonamides were given to pregnant rats and mice at high oral doses. Usefulness of sulfonamides is limited due to increasing frequency of resistant organisms. Sulfonamide associated deaths were reported from hypersensitivity, agranulocytosis, aplastic anemia, other blood dyscrasias. Early clinical indications may be sore throat, fever, pallor, purpura, jaundice.

Discontinue on evidence of systemic toxicity.

PRECAUTIONS

Give with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Maintain adequate fluid intake to prevent crystalluria and stone formation. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. (Frequently dose related.)

ADVERSE REACTIONS

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme (Stevens-Johnson Syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis.

Gastrointestinal reactions: Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia.

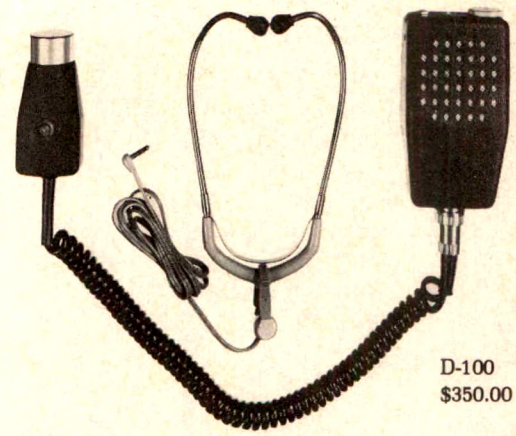
Misc.: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosum and L.E. phenomenon. Sulfonamides bear chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely. Cross-sensitivity may exist with these agents.

Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides. Long-term administration has produced thyroid malignancies in the species.

SYNTEX

SYNTEX LABORATORIES, INC.
PALO ALTO, CALIFORNIA 94304

Wear the Pocket Sonicaid For 14 Days



D-100
$350.00

Let it prove its value — or return it prepaid without obligation or other charges.

Sonicaid's most portable ultra sound fetal heart detector goes wherever you go. Loop its built-in cord around your neck; clip it to the belt or pocket. The sensitive, reliable D-100 detects fetal heart beat as early as the 10th week. Loudspeaker for group listening; stethoscope-style headset automatically disconnects speaker for privacy. Other applications include: early diagnosis of multiple pregnancy; location of placenta prior to amniocentesis; and identification of umbilical cord flow.

Two Models

Choose the 9V* battery, non-rechargeable model, or the nickel-cadmium battery, rechargeable model. The recharger, which plugs into the transducer fitting, can serve an entire office's D-100's.

* available at any drugstore

Equip yourself and your entire staff. Order here. Now.

Name_____

Address _____

City, State, Zip_____

Please send me the following D-100 units:

Non-rechargeable Model D-100 9V, battery	____ quantity	@ $350 =	____ amount
Rechargeable Model D-100 R nickel-cadmium battery	____ quantity	@ $350 =	____ amount
R100 Recharger for D-100 R	____ quantity	@ $45 =	____ amount
			____ TOTAL

☐ Check enclosed ☐ Bill me at address above

☐ Bill me at address here: _____

All units shipped complete with transducer, stethoscope headset, batteries, coupling medium and instruction manual.

SONICAID

P.O. Box 714 FF, Fredericksburg, VA 22401, (703) 898-6820

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY
TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.
A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

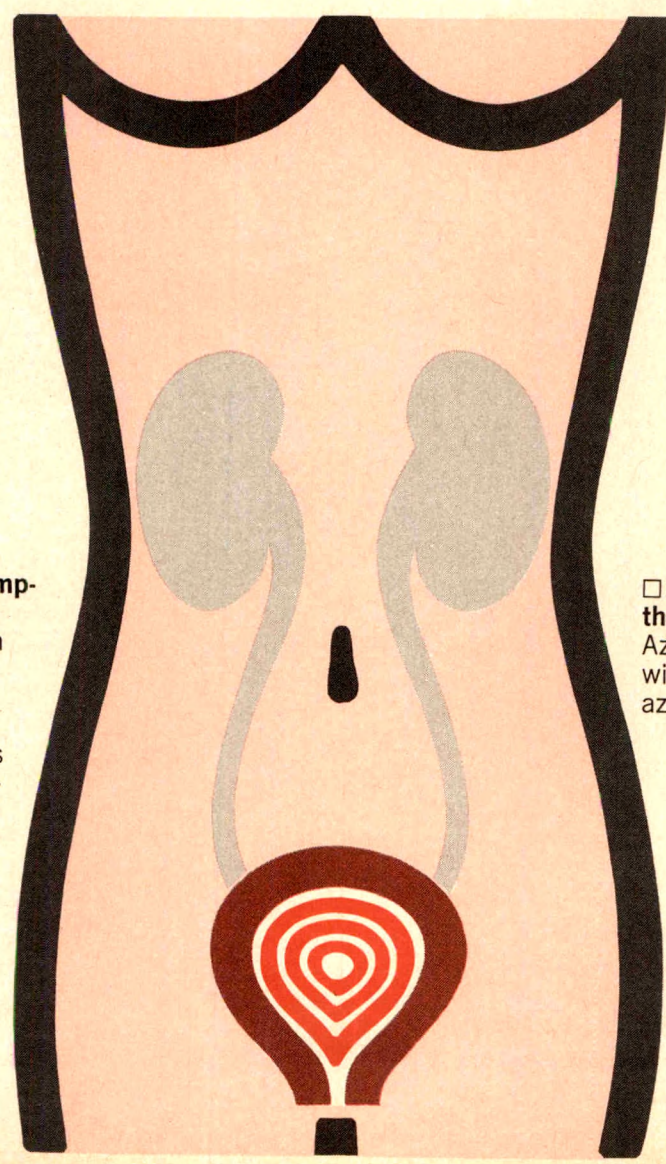
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

When pain complicates acute cystitis*

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain for the pathogens



☐ **Early relief of painful symptoms** such as burning and discomfort associated with urgency and frequency.

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

☐ **Appropriate antibacterial therapy:** up to three days with Azo Gantanol, then 11 days with Gantanol® (sulfamethoxazole).

*nonobstructed; due to susceptible organisms

ROCHE

No. 3
As potent as the pain it relieves.

e.g. postpartum pain



NOT TOO LITTLE
- as potent as the pain you need to relieve in patients with fractures, sprains, strains, wounds, contusions, and the pain of surgical convalescence
- unlike acetaminophen/codeine combinations, it does not sacrifice anti-inflammatory action

NOT TOO MUCH
- potent—yet not excessive
- addiction liability low

NOT TOO EXPENSIVE
- brand-name quality, yet reasonable in cost
- readily available in both hospital and local pharmacies

CIII CONVENIENCE
- telephone Rx in most states, up to 5 refills in 6 months at your discretion (where state law permits)

EMPIRIN® COMPOUND WIT CODEINE NO. 3

codeine phosphate* (32.4 mg) gr ½
Each tablet also contains: aspirin gr 3½, phenacetin gr 2½, caffeine gr ½. *Warning—may be habit-forming.

Wellcome | Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

November 1

1976

Transactions of the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists

Cesarean section in present-day obstetrics 521

O. Hunter Jones, M.D.

Charlotte, North Carolina

Accurate amniotic fluid bilirubin analysis from the "bloody tap" 531

Charles J. Hochberg, M.D., Alan P. Witheiler, Ph.D., and Helen Cook, M.T.-ASCP

Tampa, Florida

The individual at high risk for endometrial carcinoma 535

Saul B. Gusberg, M.D.

New York, New York

(Contents continued on page 7)

Vol. 126, No. 5, November 1, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.

The causes of vaginitis are multiple



You can depend on AVC... therapy that combats major vaginal pathogens and provides rapid symptomatic relief.*

***Indications:** Based on a review of AVC by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually *Trichomonas vaginalis*, *Candida albicans*, or *Hemophilus vaginalis*) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Known sensitivity to sulfonamides.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.

Dosage: 1 applicatorful (about 6 g.) or 1 suppository intravaginally once or twice daily.

Supplied: Cream–4 ounce tube with applicator.
Suppositories–Box of 16 with inserter.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

4-6744 (6049)

The treatment is singular

AVC™

Cream (aminacrine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%)

Suppositories (aminacrine hydrochloride 0.014 g., sulfanilamide 1.05 g., allantoin 0.14 g.)

Contents continued from page 5

Cancer risk in diethylstilbestrol-exposed offspring 543
Richard F. Mattingly, M.D., and Adolf Stafl, M.D., Ph.D.
Milwaukee, Wisconsin

A comparison of oral prostaglandin E_2 and intravenous oxytocin for induction of labor in normal and high-risk pregnancies 549
George H. Nelson, Ph.D., M.D., and C. I. Bryans, Jr., M.D.
Augusta, Georgia

A standard of fetal growth for the United States of America 555
William E. Brenner, M.D., David A. Edelman, Ph.D., and
Charles H. Hendricks, M.D.
Chapel Hill and Research Triangle Park, North Carolina

Combined outpatient laparoscopic sterilization with therapeutic abortion 565
C. Edwin Powe, Jr., M.D., and John A. McGee, Jr., M.D.
Charlotte, North Carolina

A new look at pelvic relaxation 568
A. Cullen Richardson, M.D., James B. Lyon, M.D., and
Nancy L. Williams, B.S., R.N.
Atlanta, Georgia

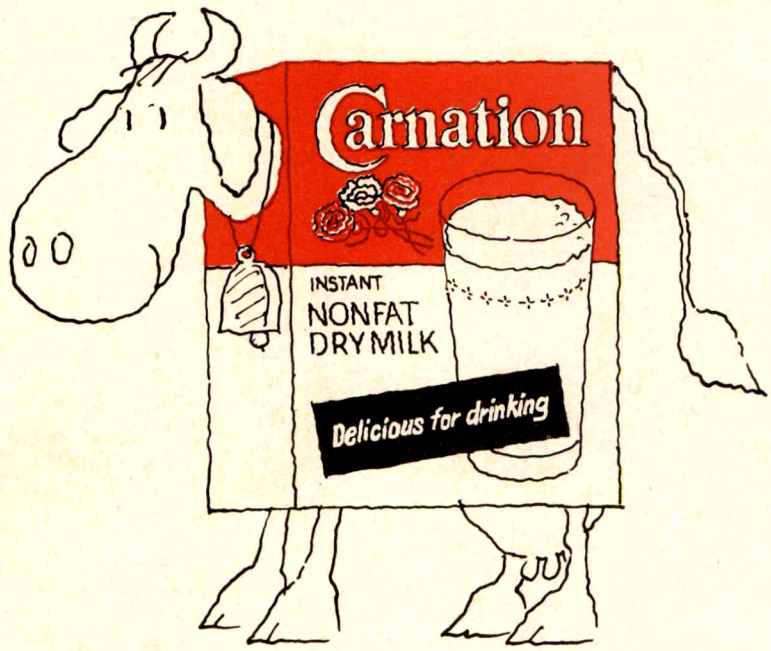
***Corynebacterium vaginale (Haemophilus vaginalis)* in women with leukorrhea** 574
William E. Josey, M.D., William J. McKenzie, M.D., and
Dwight W. Lambe, Jr., Ph.D.
Atlanta, Georgia

Gonadoblastoma: Clinicopathologic correlation in six patients 579
H. Oliver Williamson, M.D., Paul B. Underwood, Jr., M.D.,
Albert Kreutner, Jr., M.D., J. Felix Rogers, M.S.,
Rajesh S. Mathur, Ph.D., and H. Rawling Pratt-Thomas, M.D.
Charleston, South Carolina

Clinical experience with the copper-7 intrauterine contraceptive device 586
William A. Nebel, M.D., John L. Currie, M.D., and Richard E. Lassiter, M.D.
Chapel Hill, North Carolina

A composite vaginal vault suspension using fascia lata 590
John H. Ridley, M.D.
Atlanta, Georgia

(Contents continued on page 9)



We've gone the cow one better.

Carnation Instant Nonfat Dry Milk has taken all the good parts of whole milk like protein, calcium and B-vitamins — and has eliminated the bad... like fat.

In addition, Carnation Instant Nonfat Dry Milk is fortified with vitamins A and D. And since it starts out dry, you can control the balance of protein and solids to suit any low-fat diet. We even have these free diet plans to make things better:

1. Reducing
2. Pregnancy Weight Control
3. Low Sodium
4. Cholesterol Control for Weight Reduction
5. Cholesterol Control for Normal Weight Patients
6. Diabetic
7. Bland Ulcer

We can't think of a reason not to prescribe Carnation Instant Nonfat Dry Milk to all of your patients.

For a free supply of any of the diet plans listed, circle the corresponding number (s) 1, 2, 3, 4, 5, 6, 7. Send completed coupon to:
Carnation Company, P.O. Box 550
Dept. 6B4, Pico Rivera, Calif. 90665

Name_____
Address_____
City_____
State_____ Zip_____

Contents continued from page 7

Classic pages

Classic pages 597

Current developments

The critical control of progesterone levels and pregnancy by antiprogesterone 598

A. I. Csapo and T. Erdos

St. Louis, Missouri, and Gif-sun-Yvette, France

Hepatitis B antigen: A review of its importance in the practice of obstetrics and gynecology 602

Richard R. Babb, M.D.

Palo Alto, California

Correspondence

Correspondence 607

Items

Items 626

(Information for authors on page 19)

(Business communications on page 21)

ANTISEPTIC SECURITY

in Ob/Gyn practice

Prompt, broad-spectrum action of BETADINE Microbicides provides topical antiseptic security for patients, physicians and nurses

BETADINE Solution Microbicidal Applicator, the only 8½″ long, disposable antiseptic-impregnated swabstick, is indicated for degerming hard-to-reach sites, such as the cervix, vulvovaginal, perineal and anorectal areas

BETADINE Solution, for prepping skin, vagina and perineum, and for general antiseptic use on skin, mucosa and wounds

BETADINE Surgical Scrub, for preoperative scrubbing and for hand and skin degerming (In the rare instance of local irritation or sensitivity, discontinue use in the individual)

BETADINE Douche, for treating vaginal moniliasis, *T. vaginalis* vaginitis and nonspecific infectious vaginitis (*H. vaginalis* vaginitis)... also ideal for routine cleansing, due to its degerming and deodorizing properties

Purdue Frederick

© COPYRIGHT 1975, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A8076 168875



BETADINE® Microbicides

Foremost documented broad-spectrum topical microbicides



Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

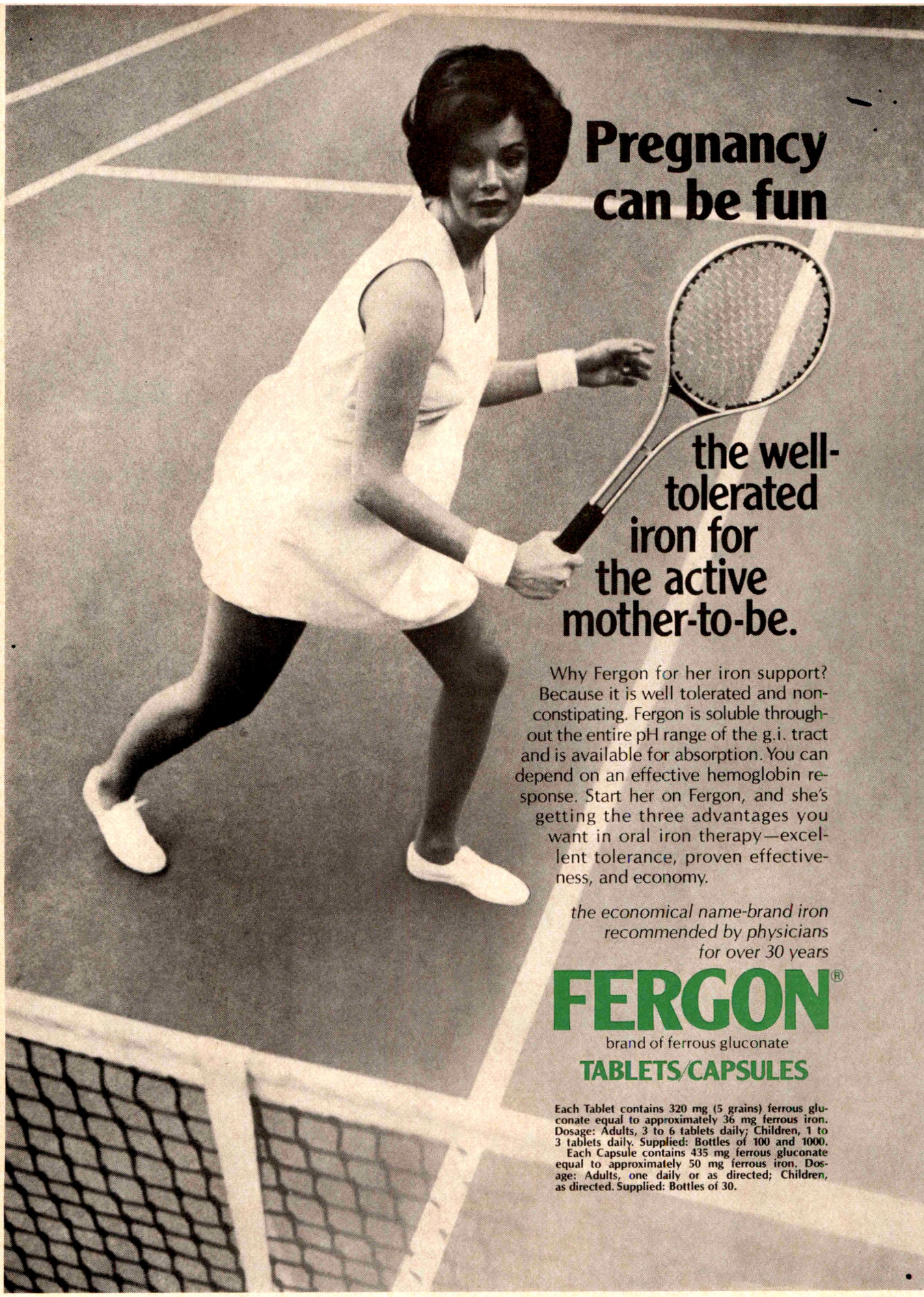
HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

Advisory committee on policy

David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*



Pregnancy can be fun

the well-tolerated iron for the active mother-to-be.

Why Fergon for her iron support? Because it is well tolerated and non-constipating. Fergon is soluble throughout the entire pH range of the g.i. tract and is available for absorption. You can depend on an effective hemoglobin response. Start her on Fergon, and she's getting the three advantages you want in oral iron therapy—excellent tolerance, proven effectiveness, and economy.

the economical name-brand iron recommended by physicians for over 30 years

FERGON®

brand of ferrous gluconate

TABLETS/CAPSULES

Each Tablet contains 320 mg (5 grains) ferrous gluconate equal to approximately 36 mg ferrous iron. Dosage: Adults, 3 to 6 tablets daily; Children, 1 to 3 tablets daily. Supplied: Bottles of 100 and 1000.

Each Capsule contains 435 mg ferrous gluconate equal to approximately 50 mg ferrous iron. Dosage: Adults, one daily or as directed; Children, as directed. Supplied: Bottles of 30.

BREON **BREON LABORATORIES INC.,** Subsidiary of Sterling Drug Inc., 90 Park Avenue, New York, N.Y. 10016

American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS
AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY

Comprehensive Group Health Care Plan

(Winston-Salem, North Carolina)

A new prepaid group health plan (Multi-specialty) opened July, 1976, for employees of R.J. Reynolds Industries, Inc. Assured growth, continuing expansion. The following board-qualified specialists are needed:

INTERNISTS PEDIATRICIANS OB/GYN

This represents an opportunity to practice under ideal conditions in modern new facilities and excellent hospitals. Medical school environment.

Winston-Salem is located in the Piedmont section of North Carolina and is within reasonable driving distances to the Atlantic Ocean and Blue Ridge Mountains. The city is noted for its cultural, recreational, and college environments.

Salary commensurate with experience. Liberal fringe benefits including paid vacation, CME, retirement, life insurance, and health coverage. Malpractice insurance paid. Relocation expenses paid.

Send curriculum vitae, including salary requirements to:

Reid Bahnson, M.D.
Medical Director
W-S HEALTH CARE PLAN, INC.
250 Charlois Blvd.
Winston-Salem, North Carolina 27103

Winston-Salem Health Care Plan Inc.

An Equal Opportunity Employer M/F

Community Hospital will sponsor first year of private, solo practice for OB-GYN. Prefer someone finishing Residency in June, 1977. Guaranteed income, paid move, malpractice insurance paid and rent-free office and equipment. Please include C. V. Reply Box AJOG-3.



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼″ × 11″) for 1975 copies
☐ OLD SIZE (7¼″ × 10½″) for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

Mead Johnson announces

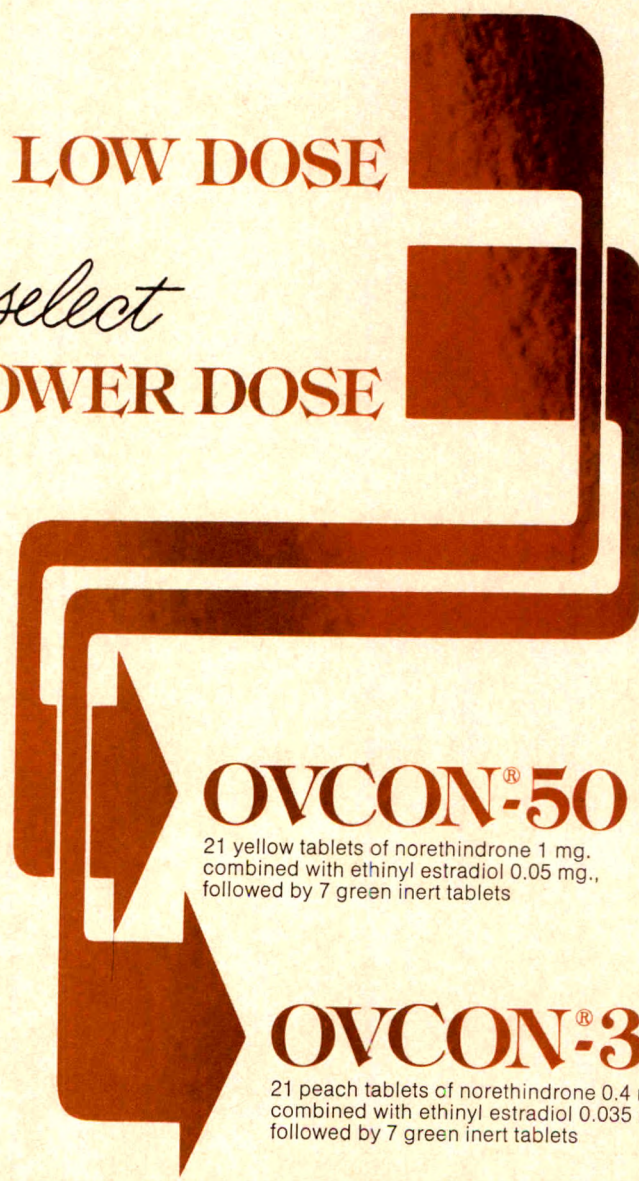
OVCON®

ne name to remember
n low-dose oral contraceptives

wo doses
rom which to select

LOW DOSE

LOWER DOSE



OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

OVCON®-35*

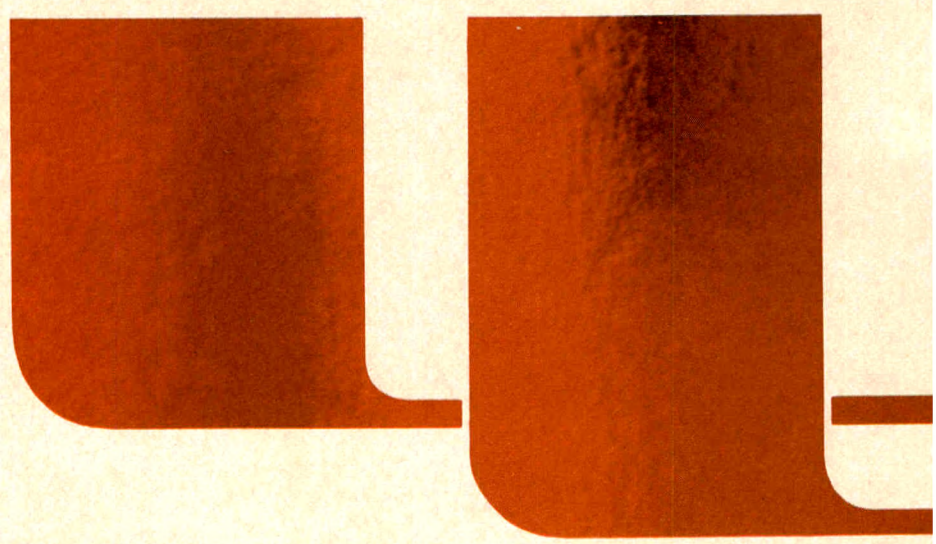
21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

Brief Summary, please see last page of this advertisement.

One name to remember in combination oral contraceptive effectiveness...

OVCON®

two doses from which to select



providing...

- effective low-dose contraceptive protection*
- low incidence of common side effects†
- acceptable cycle control†
- in-depth clinical studies in widely different populations

Mead Johnson LABORATORIES

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

tested in 1,028 women for 9,558 cycles[1]

Although these women represented a wide range of socioeconomic groups with inherent differences in motivation, pregnancy rate (Pearl's formula) was 0.13 pregnancies per 100 woman years due to method failure and 0.75 pregnancies per 100 woman years due to patient failure. This results in a use-effectiveness of 0.88 pregnancies per 100 woman years.

Few women—2.7%—discontinued therapy for cycle-related reasons . . . and these were not necessarily spotting or breakthrough bleeding, but included amenorrhea and what women considered bleeding too little or too much. There was a discontinuation rate of 10.8% for all other on-therapy conditions, which, however, were not necessarily caused by Ovcon-50.

OVCON®-35*

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

tested in 1,861 women for 20,230 cycles[1]

In these women, with a wide range of backgrounds and motivations, there was effective control of conception. Pregnancy rate (Pearl's formula) due to method failure was 0.41 pregnancies per 100 woman years, and 0.95 pregnancies per 100 woman years were due to patient failure. This results in a use-effectiveness of 1.36 pregnancies per 100 woman years.

There was a higher discontinuation rate —11.6%—for cycle-related reasons with Ovcon-35 than with Ovcon-50, but, again, reasons included any spotting as well as amenorrhea and bleeding too much, too little, or irregularly. On the other hand, the discontinuation rate for all other on-therapy conditions, which were not necessarily related to Ovcon-35, was quite low—7.1%.

1. Data on file, Mead Johnson Laboratories.

OVCON-50 and OVCON-35* offer the advantages of effective low-dose protection and of uninterrupted regimens— 21 active tablets and 7 inert tablets

For Brief Summary, please see following page.

*The effectiveness of Ovcon-35 is somewhat lower than higher-dose combination products.

†See "Special Note" section of prescribing information on last page of this advertisement.

two dosages from which to select

LOW DOSE
OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets.

LOWER DOSE
OVCON®-35

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. The effectiveness of OVCON-35 is somewhat lower than higher-dose combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons due to menstrual disorders and irregularities appears to be higher for OVCON-35 than that observed with higher-dose combination products. An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Oral contraception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen dependent neoplasia; undiagnosed abnormal genital bleeding; known or suspected pregnancy.

Warnings: If signs of thrombotic and thromboembolic disorders (thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis) occur or are suspected, use of the drug should be discontinued immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug use was discontinued and not enhanced by long-term use.[1-10]) If gradual or sudden, partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11-13] Safety of use in pregnancy has not been established, therefore pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant cannot be determined at this time. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in short-term as well as long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

Precautions: A thorough history and physical examination of breasts and pelvic organs should include Papanicolaou smears. (Estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after the drug has been withdrawn for two months. Under the influence of these drugs, pre-existing uterine fibromyomata may increase in size. Some conditions (epilepsy, migraine, asthma, cardiac or renal dysfunction) might be influenced by fluid retention. Observe carefully for such. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged OVCON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. Diabetic patients should be carefully observed while receiving such therapy. The age of the patient constitutes no absolute limiting factor, although these drugs may mask the onset of the climacteric. The pathologist should be advised of OVCON therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. If cholestatic jaundice occurs, OVCON should be discontinued. This condition is more likely to occur in patients with a history of cholestatic jaundice of pregnancy.

Adverse Reactions Observed in Patients Receiving Oral Contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage and gall bladder disease. Suggestive evidence, neither confirmed nor refuted, between use and: neuro-ocular lesions (retinal thrombosis and optic neuritis) and hepatic lesions with or without intra-abdominal bleeding. Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps and bloating), breakthrough bleeding, change in menstrual flow, spotting, amenorrhea during and after treatment, breast changes (tenderness, enlargement and secretion), mental depression, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals, edema, chloasma or melasma (which may persist), cholestatic jaundice, migraine, rash (allergic). Reported association with use, neither confirmed nor refuted: anovulation post treatment; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; intolerance to contact lenses; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; vaginitis. *May Alter Laboratory Results in:* Hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X, decrease in anti-thrombin III and an increase in norepinephrine-induced platelet aggregability), thyroid function (increase in PBI, and butanol extractable protein bound iodine and decrease in T_3 uptake values), metyrapone test, pregnanediol determination.

References: (1) Royal College of General Practitioners: Oral contraception and thromboembolic disease. J. Coll. Gen. Pract. *13*:267-279, 1967. (2) Inman, W.H.W. and Vessey, M. P. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women in child-bearing age. Brit. Med. J. *2*:193-199, 1968. (3) Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease: A further report. Brit. Med. J. *2*:651-657, 1969. (4) Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. Thromboembolism and oral contraceptives: An epidemiologic case-control study. Amer. J. Epidem. *90*:365-380, 1969. (5) Oral contraception and increased risk of cerebral ischemia or thrombosis. New Eng. J. Med. *288* (17):871-877, 1973. (6) Oral contraceptives and stroke in young women. JAMA *231*(7):718-722, 1975. (7) Boston Collaborative Drug Surveillance Programme. Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumours. Lancet *1*:1399-1404, 1973. (8) Oral Contraceptives and Health. A summary of an interim report from the oral contraception study of the Royal College of General Practitioners, May, 1974. (9) Vessey, M. P., Doll, R., Fairbairn, A. S., and Glober, G. Post-operative thromboembolism and the use of oral contraceptives. Brit. Med. J. *3*:123-126, 1970. (10) Greene, G. R. and Sartwell, P. E. Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am. J. Public Health *62*:680-685, 1972. (11) Nora, A. H. and Nora, J. J. A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch. Envir. Health *30*:17-21, 1975. (12) Janerich, D. T., Piper, J. M., and Glebatis, D. M. Oral contraceptives and congenital limb-reduction defects. New Eng. J. Med. *291*(14):697-700, 1974. (13) Carr, D. H. Cytogenetics and malformations in abortions. Fed. Proc. *30*:102-103, 1971.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 754095

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2,* Current Investigation and Clinical Opinion, limited to *6,* and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

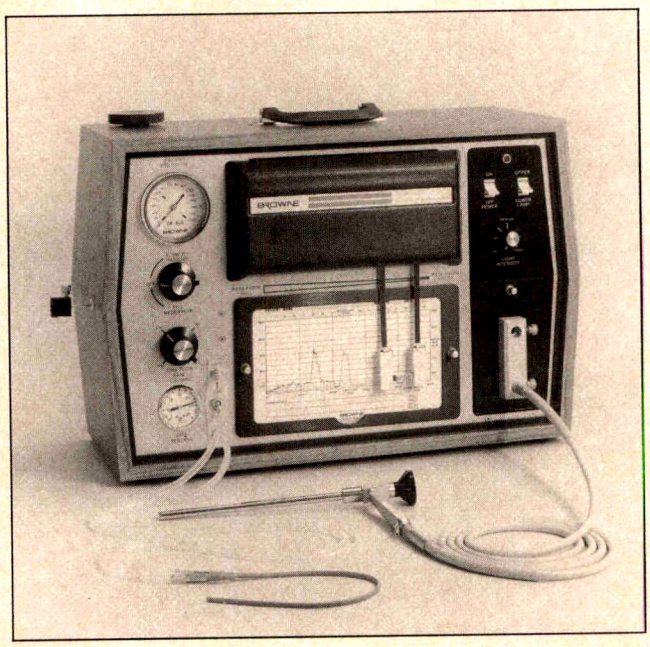
Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Lower Urinary Tract Dysfunction... ...Should You Operate?

One of the most critical decisions in any diagnosis today is whether or not to operate. Based on the most comprehensive diagnostic data available, you must make that recommendation. Browne Corporation CO_2 Endoscopy/Cystometry Monitors are designed to add significantly to that data and to present it to you in its most usable form. Consider these features:

Fail Safe Gas Supply System: Delivers CO_2 to patient at selected pre-calibrated flow rates. Three independent safety systems limit pressure and volume supplied during a single cycle. Medical grade cartridge powers both the supply and recording systems.

Automatic Catheter Puller: Synchronized with the recording system to provide direct readout of urethral length and position on the patient chart card.



Fiber Optic Illuminator: Dual 150 watt lamps with variable intensity and selector controls are provided as an option for endoscopy procedures.

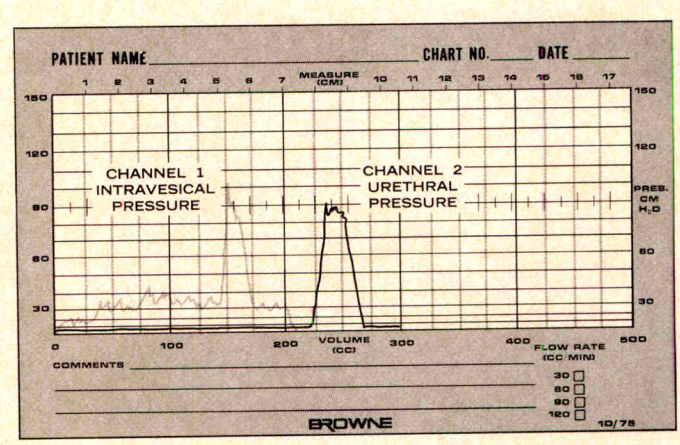
Robertson Urethrascope: Straight ahead, wide-angle field of view. Fully concentric fiber optics assure even illumination. Integral handle with fiber optic and gas fittings simplifies assembly and sterilization. Removable gas sheath, obturator and case included.

Four Function Profile Chart Recorder: Monitors total CMG volume, urethral position, intravesical pressure, and/or urethral pressure. Proprietary design is non-electrical and requires no calibration.

Cystometry And Urethral Pressure Catheters: Available in both single lumen and dual lumen versions with calibrated cm markings. Designed to attach directly to the automatic catheter puller.

Permanent Record: The exclusive patient chart card provides a clear, concise, retainable record of each procedure for historical and legal purposes. Diagnosis of complex, interacting varibles is often greatly simplified.

The sample card shown at right (one half actual size) is a simulation of a pressure/volume cystometrogram with simultaneous urethral pressure monitoring. Channel one indicates intravesical pressure spasms in excess of 100cm H_2O. Simultaneously, the Monitor's second channel has recorded a normal urethral pressure of 90cm H_2O. This patient's urinary incontinence is probably due to an uninhibited neurogenic bladder. A simple in-office procedure has ruled strongly against surgical candidacy.



To arrange a demonstration of the Browne Endoscopy/Cystometry Monitor, please write to us at Browne Corporation, 203 Chapala Street, Santa Barbara, Calif. 93101, or call (805) 963-0371.

BROWNE CORPORATION

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Editors Emeritus

Howard C. Taylor, Jr.
200 E. 66th St., New York, New York 10021

Allan C. Barnes
111 W. 50th St., New York, New York 10020

Publisher

The C. V. Mosby Company
11830 Westline Industrial Drive
St. Louis, Missouri 63141

Entered at the Post Office at St. Louis, Mo., and additional mailing offices as Second-class matter.

Business communications

Business communications. All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the Publisher, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Publication order. The semimonthly issues of this Journal form three volumes per year; the index is in the last issue of the volume—in the April 15, August 15, and December 15 issues.

Change of address notice. Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, the name of this Journal, and the full form of both old and new addresses, including the ZIP code number.

Advertisements. Forms close 25th of second previous month for the 1st of month issue; 15th of preceding month for the 15th of month issue. Advertising rates and page sizes will be given on application. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Bound volumes. Publishers' Authorized Bindery Service, 4440 West Roosevelt Road, Chicago, Illinois 60624, will quote prices for binding complete volumes in permanent buckram.

Published semimonthly

Subscriptions may begin at any time.

TENTH ANNUAL POSTGRADUATE COURSE

Gynecologic Pathology,
Cytogenetics, Endocrinology

The 10th Annual Postgraduate Course in Gynecologic Pathology, Cytogenetics, and Endocrinology will be held at the Pfister Hotel and Tower, Milwaukee, Wisconsin, from March 23-30, 1977. This 6-day course, which is limited to 150 applicants, is designed primarily as a postgraduate refresher course for residents, practitioners, and specialists desiring a current review of the pathophysiology of the reproductive tract. This course has been approved for 50 cognate hours of prescribed credit by the American College of Obstetrics and Gynecology. It has also been approved for 43 hours of credit in Category I for the Physicians Recognition Award of the American Medical Society. A $400.00 enrollment fee, payable to The Medical College of Wisconsin, will include 60 selected Kodachrome 35 mm. slides. The registration fee is nonrefundable. Guest faculty will include H. W. Jones Jr., M.D., Georgeanna S. Jones, M.D., E. R. Novak, M.D., J. D. Woodruff, M.D., and C. G. Julian, M.D.

For further details and registration, write to: Richard F. Mattingly, M.D., The Medical College of Wisconsin, 8700 W. Wisconsin Avenue, Milwaukee, Wisconsin 53226.



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

- -

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

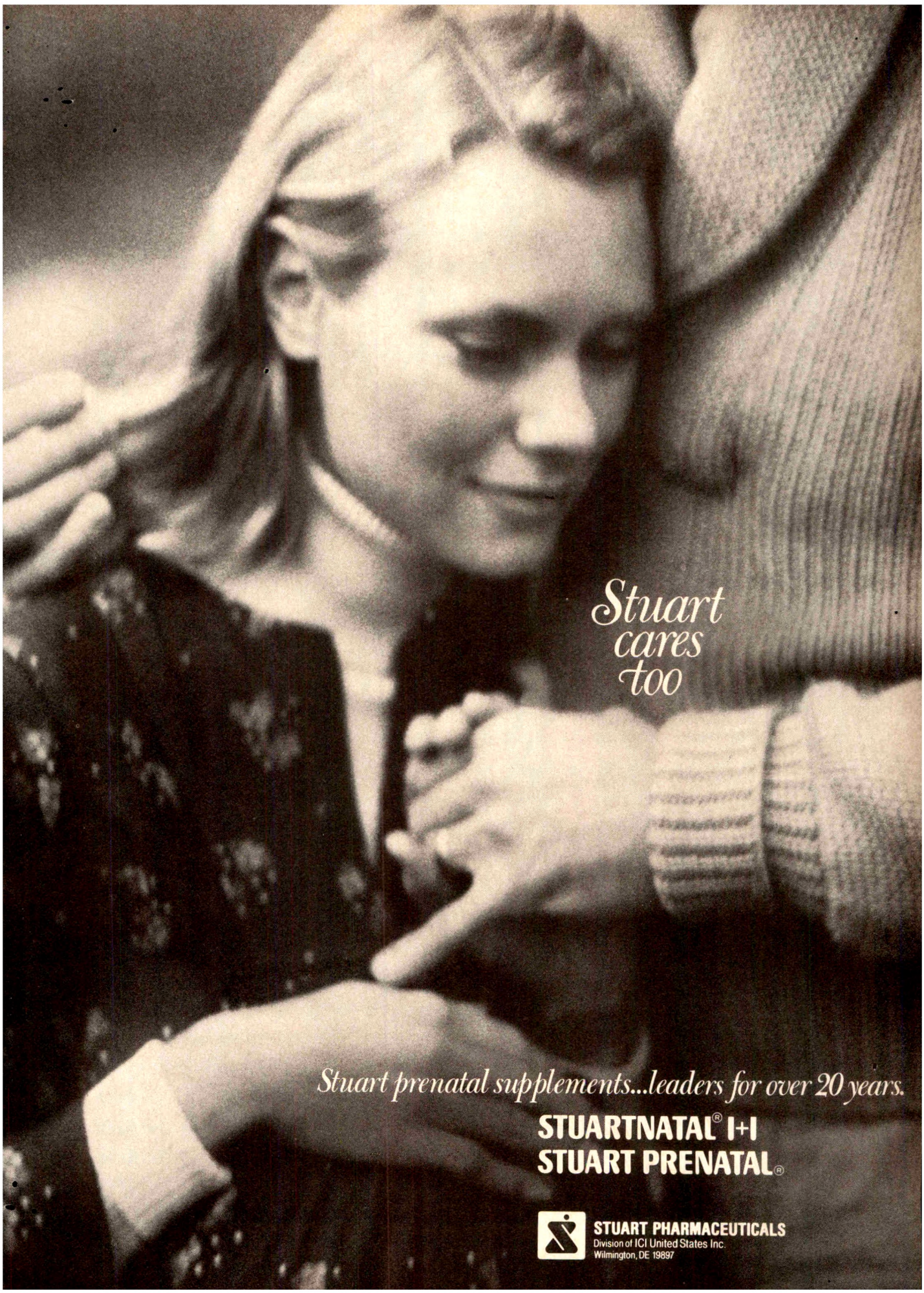
Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼" × 11") for 1975 copies**
☐ **OLD SIZE (7¼" × 10½") for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____


Stuart
cares
too
Stuart prenatal supplements...leaders for over 20 years.
STUARTNATAL® I+I
STUART PRENATAL®
STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, DE 19897

EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1695 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6″ × 9″. Price, $9.95.

Please send me on 30-day approval **THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.** Price, $9.95.

☐ Bill me ☐ Master Charge #_____

☐ Payment enclosed

Name _____

Address _____

City _____

State _____ Zip Code _____

MOSBY

TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.

A60519

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

IN MONILIASIS BETADINE® Microbicides Vaginitis Regimen

Full Prescribing Information
BETADINE® Vaginal Gel
(povidone-iodine)

BETADINE Vaginal Gel (povidone-iodine) makes available elemental iodine in a form that maintains iodine's microbicidal activity, yet is virtually nonirritating, nontoxic and is nonstaining to skin and natural fabrics.

- Kills trichomonas, monilia, and other iodine-susceptible vaginal organisms responsible for specific and nonspecific vaginal infections.
- Active in the presence of blood, pus, or vaginal secretions.
- Virtually nonirritating to vaginal mucosa.
- Nonstaining to skin, linen or clothing of natural fabrics; color can be washed off with water.

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

Recommended regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution.

Prescribe BETADINE Vaginal Gel (povidone-iodine) as follows: Insert one (1) applicatorful each night, followed the next morning by BETADINE Douche in its therapeutic concentration (2 tablespoonfuls to a quart of lukewarm water).

This regimen is to be followed through the entire menstrual cycle, including the days of menses. If further therapy is warranted, the regimen should be continued through the next two cycles. The patient may be instructed to return for an office visit following two weeks of therapy.

Precaution

If irritation, redness or swelling develop, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

Recommended dosage

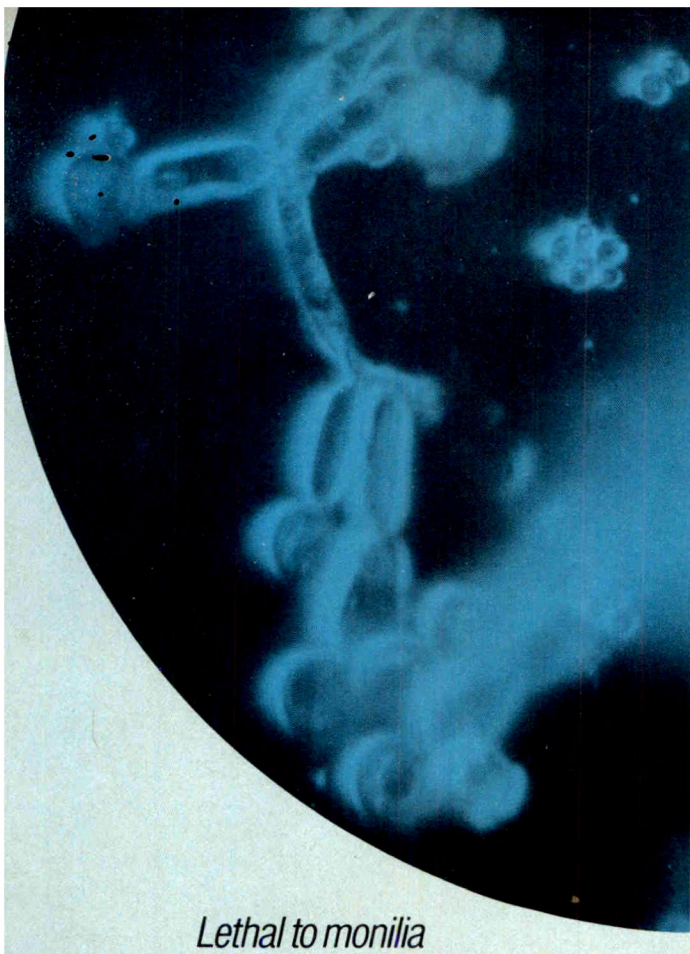
One applicatorful (5 Gm.). Each five grams (one applicatorful) is equivalent to fifty milligrams of available iodine.

Supplied

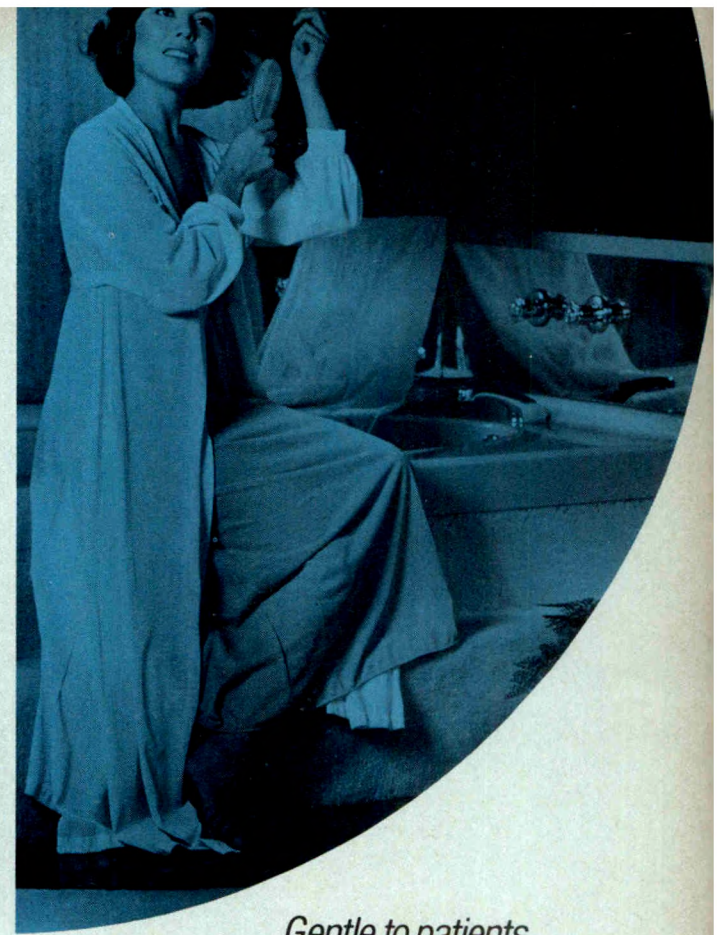
18 Gm. and 3 oz. tubes with applicator.
Only on prescription.

Purdue Frederick

©COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A9201 171276



Lethal to monilia



Gentle to patients

IN MONILIASIS

BETADINE® Microbicides Vaginitis Regimen

High cure rate... rapid symptomatic relief

High cure rate is achieved in monilial vaginitis with the topical regimen employing BETADINE Microbicides:

BETADINE® SOLUTION
BETADINE® VAGINAL GEL*
(povidone-iodine)
BETADINE® DOUCHE

Easy-to-follow regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution which is promptly and decisively microbicidal. Prescribe BETADINE Vaginal Gel (povidone-iodine), one applicatorful of which is to be inserted each night, followed the next morning by BETADINE Douche in therapeutic concentration —2 tablespoonfuls to a quart of lukewarm water.

After 2 weeks

The patient returns for an office visit after two weeks of therapy. In more resistant cases, the regimen may have to be continued through 1 or 2 cycles. BETADINE Microbicides are virtually nonirritating to vaginal mucosa and do not stain skin and natural fabrics.

Lethal to other vaginal pathogens too

The broad-spectrum microbicidal action of BETADINE Microbicides kills not only monilia, but also *Trichomonas* and *Hemophilus vaginalis.*

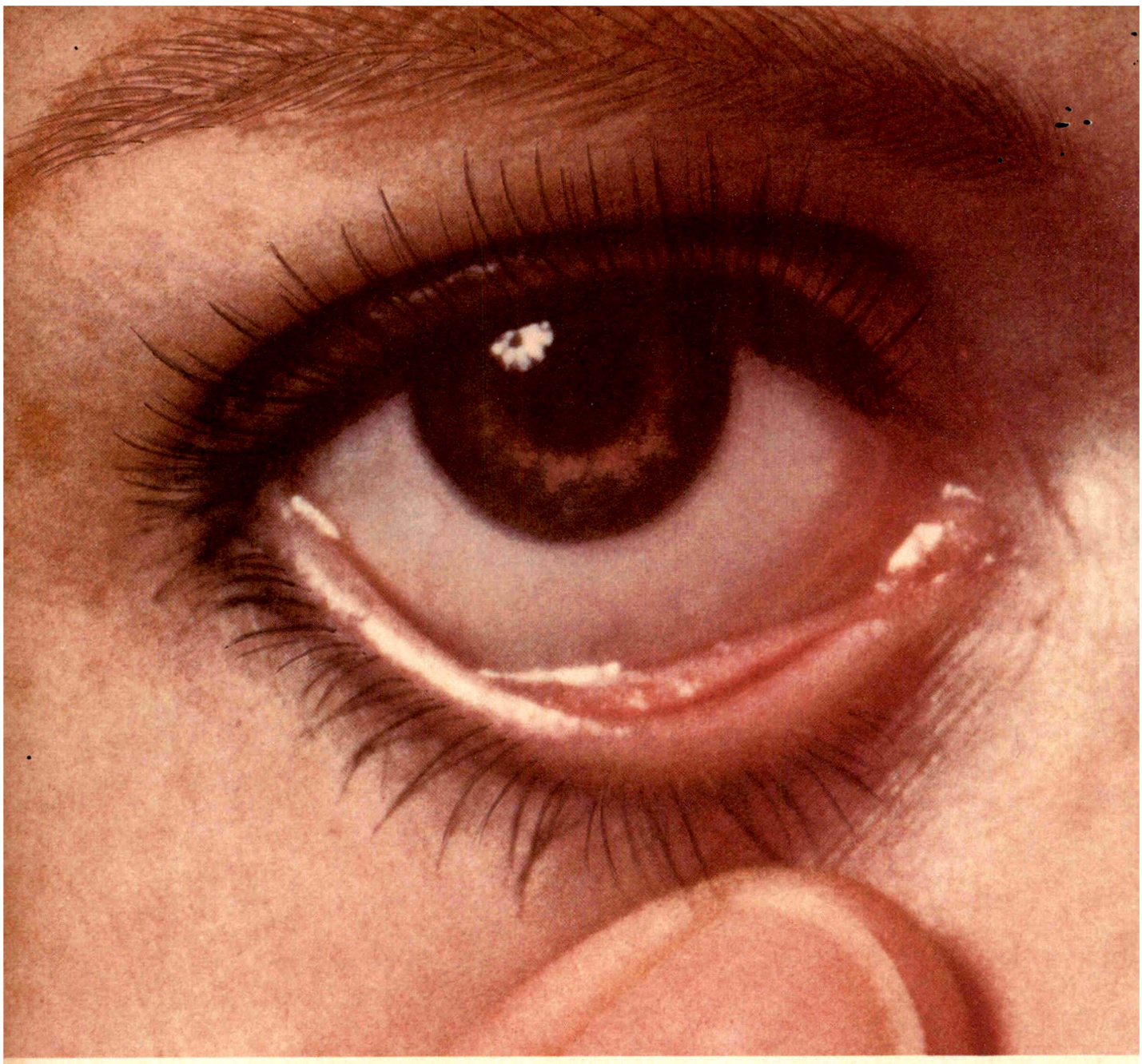
Unlike exclusively antimonilial agents, the BETADINE MICROBICIDES VAGINITIS REGIMEN is not contraindicated when *Trichomonas* or *H. vaginalis* is present.

BETADINE Microbicides kill both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts. Their microbicidal action is maintained in the presence of blood, serum, and vaginal secretions.

*BETADINE Vaginal Gel (povidone-iodine) has been evaluated as possibly effective for use in the management of *Trichomonas vaginalis* vaginitis, monilial vaginitis and nonspecific vaginitis.

Purdue Frederick

See adjoining page for full prescribing information. A8335 178376



Which hematinic works best? –the one that she takes.

Unfortunately, many women do not take their hematinics.

A majority of pregnant women fail to ingest oral iron supplements because of intolerance to oral iron and resistance to multiple daily dose regimens.*

By minimizing the chances of gastric upset and simplifying dosage (once-a-day), Abbott hematinics encourage compliance.

COMFORT—the Gradumet® controlled-release of iron takes place primarily in the small intestine where absorption of iron is greatest with minimal chance of gastric upset

COOPERATION—once-a-day dosage assures optimal patient acceptance.

CONVENIENCE—500 mg. of Vitamin C to enhance iron absorption is combined with iron and B-Complex in a single tablet.

6093160R1

Iberet®-500

Hematinic Supplying Controlled-Release Iron with Vitamin C and B-Complex (contains no folic acid)

*Kitay, D. Z., Contemporary Ob/Gyn, 2:17, 1973.

Iberet-Folic-500® ℞

Controlled-Release Iron with Vitamin C and B-Complex including Folic Acid

Please see opposite page for Brief Summary.

ABBOTT

Iberet®-500

One Filmtab® tablet a day supplies:

Controlled-Release Iron

Ferrous Sulfate,
(equivalent to
elemental iron—105 mg.) .. 525 mg.

Plus High Potency Vitamin C

Vitamin C
(as Sodium Ascorbate) .... 500 mg.

Plus the B-Complex
(contains no folic acid)

Niacinamide ..... 30 mg.
Calcium Pantothenate ..... 10 mg.
Vitamin B_1
(Thiamine Mononitrate)..... 6 mg.
Vitamin B_2 (Riboflavin) ..... 6 mg.
Vitamin B_6
(Pyridoxine Hydrochloride) .. 5 mg.
Vitamin B_{12}
(Cyanocobalamin) ..... 25 mcg.

INDICATIONS: For conditions in which iron deficiency occurs concomitantly with deficient intake or increased need for the B-complex vitamins (contains no folic acid).

Iberet-Folic-500® ℞

One Filmtab tablet a day supplies the same formula as Iberet-500 plus:

Folic Acid .....800 mcg.

INDICATIONS: In non-pregnant adults, for the treatment of iron deficiency and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins. Also indicated in pregnancy for the prevention and treatment of iron deficiency where there is a concomitant deficient intake or increased need for B-complex vitamins (including folic acid).

CONTRAINDICATION: Pernicious anemia.

WARNINGS: Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

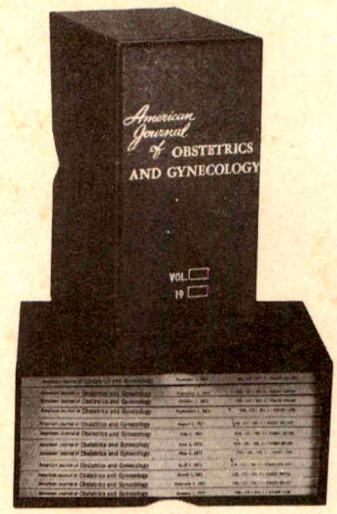
PRECAUTION: Where anemia exists, its nature should be established and underlying causes determined. Iberet-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS: The likelihood of gastric intolerance is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

6093160

• Gradumet®—Controlled-release dose form, Abbott.
Filmtab—Film-sealed tablets, Abbott.

ABBOTT



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ **NEW SIZE (8¼" × 11") for 1975 copies**
☐ **OLD SIZE (7¼" × 10½") for copies prior to 1975**

Name _____

Address _____

City _____ State _____ Zip _____





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll, R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. *3*:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 5 NOVEMBER 1, 1976

Transactions of the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists

Cesarean section in present-day obstetrics

Presidential address

O. HUNTER JONES, M.D.

Charlotte, North Carolina

Two thousand five hundred and sixty-three cesarean sections performed at Charlotte Memorial Hospital during 1963 through the first six months of 1975 were reviewed. The cesarean section rate was 6 per cent. The results of two earlier studies, starting with the opening of the hospital in 1940, were compared. The total number of cesarean sections from 1940 through 1975 was 3,717. The present study shows that significant improvement has been made in reducing cesarean section deaths, morbidity, and complications, as well as fetal deaths. There have been no maternal deaths in the last 2,225 cesarean sections. Questionnaire returns from 50 representative medical schools and obstetricians throughout the United States discuss the increased cesarean section rate, the reasons for the increase, and the predicted cesarean section incidence of the future.
(AM. J. OBSTET. GYNECOL. 126: 521, 1976.)

THE CESAREAN SECTION RATE in Charlotte Memorial Hospital from November 1, 1962, to July 1, 1975, was 6 per cent (private, 6.8 per cent; staff, 5.3 per cent). Table I shows the rate since the hospital opened in late 1940.[1, 2]

The rate for private patients has always been higher than the staff rate, much more in the earlier years than recently. In the present study, Florence Crittenton Home (F.C.H.) patients provided 13 per cent of total staff deliveries, with a cesarean section rate of 2.6 per cent. Contrary to the prevailing attitude of the past, today the indication for cesarean section is just as valid for the single patient as for the married patient (i.e., the F.C.H. cesarean section rate for the past five years has averaged 4.9 per cent). Since 1970, 23 per cent of all cesarean sections have been in single girls (approximately one sixth from F.C.H.); 91 per cent were in black patients, and 9 per cent were in white patients. The oldest was 34 years old and the youngest was 12 years old. To express it another way, since 1970, 20 per cent of all cesarean sections have been in single girls not from the F.C.H. Obviously, there is a sociologic problem involved here—one with which our society ought to come to grips!

In 1970, a change in attitude toward the indications for cesarean section took place, and the rate increased to 6.3 per cent (private, 7 per cent; staff, 6.3 per cent). From 1970 through June, 1975, the rate was 8.2 per

From the Department of Obstetrics and Gynecology, Charlotte Memorial Hospital.

Presidential address, presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. O. Hunter Jones, 1012 Kings Dr., Charlotte, North Carolina 28283.

Table I. Cesarean section rate (72,184 deliveries; 3,717 cesarean sections)

Years	*No.*	*Rate (%)*	*Private (%)*	*Staff (%)*	*Primary (No.)*	*Repeat (No.)*
1940-1952	458	4.5	5.3	1.8	316	142
1953-1962	696	3.7	4.3	1.6	386	310
1963-1975 (6 mo.)	2,563	6	6.8	5.3	1,813	750

Primary cesarean section rate: 1940-1952 = 3 per cent; 1953-1962 = 2 per cent; 1963-1975 (6 mo.) = 4 per cent.

cent (private, 9.1 per cent; staff, 7.5 per cent—including the rate in F.C.H. girls of 7.5 per cent). From 1972 through 1974, the rate was 9 per cent, and, for the first six months of 1975, it was 10.3 per cent. What is the explanation?

In general, an increased cesarean section incidence has been widely accepted by the specialty in recent years due to several reasons, which will be discussed, and this is certainly true at Charlotte Memorial Hospital. Also, there is no longer any reluctance in the staff service rate approaching that of the private service.

Indications for cesarean section

One thousand eight hundred and thirteen of the 2,563 sections were primary sections, and 750 were repeat sections (Table II).

Many sections had multiple indications. A frequent example was cephalopelvic disproportion (CPD) and uterine dysfunction—these were recorded under disproportion. "Relative CPD" was a term often employed. Failed forceps deliveries and/or trial forceps deliveries have also been included under disproportion. Such forceps attempts represent a mistake in judgment! X-ray pelvimetry is always performed in suspected disproportion.

Breech presentation has not been included under disproportion (if included, the primary CPD rate would be 64 per cent, which would be in great contrast to a rate of 28 per cent from 1953 to 1962 and 29 per cent from 1940 to 1952). The reason for not including breech presentation is that obstetricians no longer choose to take "any chance" with the breech, and so often the premature breech infant is delivered by elective cesarean section. Thus, it hardly seems correct to include all breech presentations under true disproportion, although many cases would qualify.

Fetal distress is over three times greater than in the two previous studies as a result of improved methods of fetal heart monitoring. The original Doptone introduced in the late 1960's and the Corometrics monitoring system* developed in the early 1970's have added considerably to the increase in the cesarean section rate, not only in total numbers but also in the better selection of cases.

Severe pre-eclampsia and eclampsia remain with us—obviously the solution for this has not yet been found.

Today, an indication for cesarean section is placental insufficiency as determined by estriol studies, oxytocin challenge tests, and the human placental lactogen test. These studies, together with methods for determining fetal growth and maturity, such as ultrasound, and amniocentesis with certain biochemical tests, Rh incompatibility, and the presence of meconium, are of great help to the obstetrician in improving fetal salvage and well-being. The indications for cesarean section have been greatly broadened in recent years, and these factors help to explain the increased rate of cesarean section.

Maternal deaths

There were two maternal deaths, for a mortality rate of 0.08 per cent (cesarean section–related, 0.04 per cent) (Table III).

The only true cesarean section death was in 1965, in a primiparous staff patient 18 years old, at term and in spontaneous labor for 20 hours. Disproportion was present, and fetal distress developed, resulting in cesarean section. Local anesthesia was used until the abdomen was entered, at which time general anesthetic agents (thiopental sodium, cyclopropane, and succinylcholine) were begun. Two minutes after thiopental sodium was given, the patient regurgitated; suction was performed with great difficulty, and then intubation (uncuffed) was done. An 8 pound infant was delivered and survived. The patient died 4½ hours after cesarean section from aspiration—confirmed by autopsy. This was an inexcusable death—intubation should have been done sooner (at the present time it would have been cuffed), bronchoscopy performed, steroids administered, consultation obtained, and the residents should have remained with the patient—none of these things were done.

Thus, if the mortality rate is corrected to include only cesarean section–related deaths, the aspiration death would be the only one, for a rate of 0.04 per cent. The reduction in the maternal mortality rate at Charlotte Memorial Hospital over the past 35 years is significant. The desired goal of no deaths is perhaps

*Corometrics Medical Systems, Inc., 2 Barnes Industrial Park Rd., Wallingford, Connecticut 06492.

Table II. Indications for cesarean section, 1962 to 1975 (six months)

Repeat section	750 (29%)	
Primary section	1,813 (71%)	
Total	2,563	
Indications for primary section		
CPD (includes 35 cases of failed use of forceps, also many cases associated with dysfunctional labor-inertia)		49%
Breech		15%
Primary uterine dysfunction, inertia, cervical dystocia		3.5%
Transverse lie		3.3%
Prolapsed cord		2.8%
Placenta previa		4.6%
Abruptio placentae		3.9%
Fetal distress (also associated with 275 additional cases, i.e., CPD, breech, pre-eclampsia, etc.)		7.6%
Pre-eclampsia–eclampsia		2.4%
Diabetes		3%
Failed induction of labor		1.2%
Miscellaneous (including previous hysterotomy, incompetent cervix, postmaturity, prolonged ruptured membranes, previous vaginal plastic surgery, carcinoma of cervix, rupture of uterus, heart disease, marginal sinus rupture, placental insufficiency, positive oxytocin challenge test, herpes genitalis)		3.7%

impossible to achieve, but it is most encouraging that there have been no deaths in the last 2,225 cesarean sections.

Types of operations

Ninety-seven per cent of all cesarean sections were low-flap (all Munro-Kerr except 110 Beck). There were 56 classical cesarean sections, 30 of which were in primigravidas, and this is hard to understand. Surely the advantages of the low-flap operation outweigh the choice of the occasional classical cesarean section (even in a transverse lie, for example). In my opinion, classical cesarean section rarely should be performed.

Only 126 patients had incidental appendectomy. In discussing my 1962 paper before this Association, Dr. R. Gordon Douglas,[3] of New York Hospital, reported 400 incidental appendectomies at the time of uncomplicated cesarean sections at that institution without complication from the appendectomies. There have been no complications in our hospital. Of the 126 cases, approximately one half were private (slightly over half were mine). It is interesting that Dr. Fritz Fuchs, present Chairman at New York Hospital, stated in a personal communication that it is not the policy now to perform incidental appendectomies.

Only 17 patients had vaginal delivery following cesarean section. Thirteen were staff patients. Obviously, the attending staff believes in the dictum "once a section, always a section." The experience at the New York Hospital has shown that the history of a previous cesarean section alone does not warrant repeat section.[4] Dr. Fuchs reaffirms this policy and states that 22.2 per cent are being delivered vaginally (in 1964, the rate was 39.9 per cent). Personal experience has shown that, in carefully selected cases, vaginal delivery following certain indications for the original cesarean section can be accomplished safely. I feel that most obstetricians have a somewhat unwarranted fear of this procedure. In the present study, unsuspected partial separations of the previous scar was found in 10 cases (1.3 per cent), twice as many in low-flap as in classical cesarean sections, and usually not associated with symptoms. In addition, a thin or "weak" scar was present in 10 other cases. So, in a total of less than 3 per cent of the cases of repeat cesarean section was there any cause at all for concern regarding the integrity of the uterine scar. However, one catastrophic rupture did occur in a multiparous staff patient, 6½ months pregnant, with a previous classical section for a transverse lie; spontaneous complete rupture of the uterus occurred, resulting in stillbirth and necessitating abdominal hysterectomy.

Transfusions

Eighteen per cent (460 patients) received transfusions. This represents a great decrease from previous years. For example, 66 per cent of patients having cesarean section received transfusions in 1952, and 34 per cent received transfusions in 1962. Of the 460, 40 per cent received a single transfusion, and 60 per cent received multiple transfusions. The reduced incidence probably resulted from more awareness of transfusion reaction problems in anesthetized patients, more elective sections, and earlier sections for those in labor and/or with bleeding problems.

Table III. Cesarean section maternal mortality rates

Years	*Rate (%)*
1940-1952	0.4
1952-1962	0.3
1962-1975 (6 mo.)	0.08* (cesarean section–related, 0.04)

*Includes one death in 1966, in a multiparous staff patient, 33 years old, with chronic hypertension for over 15 years, receiving treatment. She came to the antepartum clinic only twice with blood pressures of 210/120 and 262/160; she refused hospitalization and did not return. At 7½ months, she had convulsions at home and was hospitalized with subarachnoid hemorrhage and hemiparesis; she was decerebrate, and tracheotomy was necessary. Forty-eight hours later, spontaneous but desultory labor required intravenous oxytocin stimulation and amniotomy, but cesarean section was finally necessary. Only local anesthesia was used, with delivery of a 4 pound, 8 ounce baby who survived. The patient died 35 days after cesarean section. Autopsy revealed subarachnoid hemorrhage, irreversible brain damage, and massive renal necrosis. This case has to be classified, technically, as a cesarean section death, but, in reality, it is not in any way a section–related death.

Table IV. Cesarean section complications

Complication	*No.*
Uncontrollable bleeding requiring hysterectomy	3
Postoperative bleeding (3 hysterectomies)	12
Postoperative bleeding (intra-abdominal), laparotomy	2
Vesicovaginal and rectovaginal fistula	1
Ureterovaginal fistula	1
Ureteral obstruction	1
Bladder perforation	4
Laceration of intestines	1
Pelvic abscess, incision drainage	3
Broad ligament laceration–hematoma	2
Thrombophlebitis, pelvic, suspected	2
Thrombophlebitis, lower extremity	4
Wound infection	31
Partial separation of abdominal incision (20 resutured)	30
Morbidity (significant, 12%)	33%

Complications

The standard morbidity definition of a temperature of 100.4° F. (or more) after the first 24 hours was used. If a strict hourly interpretation is applied, 49 per cent showed morbidity. However, if the conventional application is used, only 33 per cent had morbidity (Table IV). More importantly, if only significant morbidity is considered, the rate would be 12 per cent, and not over half of these cases would constitute serious morbidity. Most morbidity was due to endometritis (usually of short duration). Occasionally parametritis developed, and, of course, there were the usual complications of genitourinary tract infections and respiratory infections. As expected, there was much more morbidity in staff patients.

Much progress has been made in reducing cesarean section deaths, morbidity, and the number of major complications, and usually the operation is relatively easy and uneventful; however, cesarean section occasionally can potentially represent a major operation with all of its risks. Therefore, the indication should be valid, and the decision reasonable, based upon the best judgment possible at that particular time.

Anesthesia

In recent years most cesarean sections have been performed with general anesthesia, consisting of oxygen for five minutes before anesthesia is started, then 250 mg. of thiopental sodium, followed by an 80 mg. dose of succinyl chloride intravenously for immediate endotracheal intubation. No artificial ventilation is performed prior to intubation. After intubation, controlled ventilation is performed with a mixture of 70 per cent nitrous oxide and 30 per cent oxygen. After delivery, anesthesia is deepened by the additional injection of barbiturates or a narcotic analgesic.

General anesthesia was used in 1,904 cases. Eighty-eight per cent were delivered within 8 minutes (5 per cent in 2 minutes, 70 per cent in 3 to 6, 13 per cent in 7 to 8, and 12 per cent after 8) with 74 per cent of infants having an Apgar score of 7 to 10 (15 per cent 4 to 6; 11 per cent, 1 to 3).

This study showed that infants delivered within three minutes had an Apgar score of 7 to 10 in 77 per cent of the cases (4 to 6 in 14 per cent; 1 to 3 in 9 per cent). Thus, with the dosage employed, the results indicate little significant difference in the Apgar score whether delivery occurred within the first 3 minutes or from 4 to 8 minutes. Furthermore, there is not too much difference in the Apgar scores of infants delivered after 8 minutes, as 68 per cent had Apgar scores of 7 to 10 (18 per cent, 4 to 6; 14 per cent, 1 to 3).

It is general policy of our anesthesia department not to exceed a 250 mg. dose of thiopental before delivery. The usual dose is 200 to 250 mg.

Regarding thiopental, Fisher and Paton[5] stated: "Neonatal depression is more common with a higher induction dose; optimal interval from induction to delivery 4-8 minutes; with a 300 mg. dose almost no depression. Several investigators have noted that when the induction-delivery interval is prolonged (>8 minutes), the incidence of lower Apgar scores is increased."

There were 238 cases with local infiltration of the abdominal wall; the patient was then given thiopental and a general anesthetic. Seventy-six per cent of these infants had an Apgar score of 7 to 10 (12 per cent, 4 to 6; 12 per cent, 1 to 3). This was surprising and shows that local infiltration of the abdominal wall alone is

Table V. Fetal mortality—1963 to 1975 (6 mo.)

Total No.				91 (3.5%)
Premature	59 (18%)			
Term	32 (1.2%)			
Corrected term	9 (0.3%)			
Term deaths				32
Alive at birth			18	
Congenital anomalies incompatible with life, or difficult to survive		9		
Respiratory distress syndrome		6		
Elective section, term	2			
Associated pneumonia	1			
Associated postmaturity	1			
Associated intracranial hemorrhage	1			
Associated fetal distress	1			
Placental insufficiency		1		
Cerebral-pulmonary edema with focal hemorrhage		1		
Abruptio placentae		1		
Stillbirths			14	
Maternal splenic artery aneurysm, rupture		1		
Abruptio placentae		2		
Fetal distress		4		
Congenital anomalies		2		
Pre-diabetes–diabetes		2		
Amnionitis		2		
Intrapartum death, cause undetermined (autopsy)		1		
Possible salvage by earlier cesarean section			2	
Postmaturity (?)		1		
Intermittent fetal distress		1		
Total number autopsied			22 (69%)	

hardly necessary today with proper employment of general anesthesia.

Of course, it has long been recognized that local infiltration alone, until delivery of the baby, is the anesthesia of choice to avoid neonatal depression. This has been recently emphasized by Ranney,[6] of the University of South Dakota, who stated that not only was it the anesthesia of choice to avoid neonatal depression but also to avoid possible defects later in life. The trouble has been that patients are too uncomfortable with this technique; therefore, it is not popular, and few doctors use it. Maybe we should take a new look at this technique.

Four hundred and twenty-one patients were delivered with spinal anesthesia. Eighty-three per cent of infants had Apgar scores of 7 to 10 (10 per cent, 4 to 6; 7 per cent, 1 to 3). Significant hypotension occured in 24 per cent of the cases in the early years of the study. In 1964, prophylactic intravenous phenylephrine drip was used for a few minutes; now rapid intravenous infusion of 5 per cent dextrose before spinal administration is used. Displacement of the uterus to the left also helps. Epidural anesthesia, in selected cases, was started in 1970. Hypotension occurs, at times, with epidural anesthesia also. Incidentally, Brown and associates[7] state that lumbar epidural anesthesia may result in fetal concentration of the anesthetic agent equal to or greater than that of the mother; therefore, this technique may be inadvisable in high-risk delivery.

In the early years, spinal agents and local infiltration–thiopental–general combinations were employed much more frequently than in recent years. For example, in 1964, local-thiopental-general and spinal agents were used in 91 per cent of the cases, equally divided. However, in 1974, 88 per cent of all anesthetics were general, and there were only 11 per cent spinal and 1 per cent local-general anesthetics.

To startle us, a recent study from the Boston Hospital for Women, reported by Scanlon and colleagues,[8] suggests that a more global depression of neonatal function is associated with general anesthesia for cesarean section than is associated with spinal anesthesia, which is not reflected in the Apgar scores.

Fluothane was used in a few of the earlier cases, but it was discontinued because of uterine relaxation. Cyclopropane was used in a considerable number of the earlier cases but not at present.

In a study of this kind it is difficult to state how much effect sedation, length of labor, fetal distress, prematurity, and other complications play in Apgar scores. However, in a sample study of all 1971 sections (266 cases), 76 per cent of infants of patients in early labor had an Apgar score of 7 to 10 (10 per cent, 4 to 6; 14 per cent, 1 to 3). In labors of 5 to 15 hours, 69 per cent of infants had an Apgar score of 7 to 10 (12 per cent, 4 to 6; 10 per cent, 1 to 3). In labor beyond 15

Table VI. Indications for cesarean hysterectomy

Indication	*No.*
Carcinoma of cervix (3 invasive, 2 in situ)	5
Rupture of uterus	3
Difficult-to-control bleeding (abruptio placentae, placenta previa, suspected placenta accreta)	6
Ruptured splenic artery	1
Fibromyomas of uterus	8
Severe infection	2
Sterilization	11
Total	36

hours, 64 per cent of infants had Apgar scores of 7 to 10 (10 per cent, 4 to 6; 26 per cent, 1 to 3). For the same group, if we correlate the minutes of anesthesia with the Apgar score, 74 per cent delivered within two minutes had an Apgar score of 7 to 10, 73 per cent in 3 minutes, 80 per cent in 4 minutes, 74 per cent in 5 minutes, and from 6 minutes on it varied from 72 down to 33 per cent. Thus, for the group in labor, 4 minutes (approximately) represents the best time interval for delivery.

In cases showing fetal distress in 1971, 72 per cent of infants had an Apgar score of 7 to 10 (16 per cent, 4 to 6; 12 per cent, 1 to 3). Obviously, the fetal distress was not of long duration. Certainly prolonged fetal distress may lead to serious sequelae. Constant fetal monitoring at present, in selected cases, is leading to better selection of cases for cesarean section.

Analysis of 296 cases of cesarean section in 1974 and 1975 showed that the Pfannenstiel incision added at least one minute to delivery time. For example, with a verticle incision, 84 per cent were delivered within 6 minutes, whereas with a Pfannenstiel incision only 71 per cent were delivered within 6 minutes and 81 per cent in 7 minutes.

Fetal deaths

A total of 91 babies failed to survive (Table V). Thirty-two were term (5½ pounds or above), and 59 were premature. Included in the 59 premature babies were 13 babies with a discrepancy in the estimated stage of pregnancy and birth weight (but all were under 5½ pounds)—this, I submit, is the "gray zone" or the treacherous zone, which includes, for the most part, babies in the 3 to 5 pound class. By size many of these babies are large enough to survive but die because of the maternal pathology and/or inherent fetal predisposition or weakness. At present, premature intensive care units with improved skill and sophistication are salvaging more of these babies, and it is reasonable to assume that in the future even more will be saved.

The total fetal loss was 3.5 per cent (1.2 per cent term; 18 per cent premature). Admittedly, fetal survival statistics vary considerably, depending upon the classification used.

Eighteen of the 32 term babies were born alive. Of the 18, nine had congenital defects either incompatible with life or extremely difficult to survive—all had autopsies. Six had respiratory distress syndrome (two elective cesarean sections at term, one autopsy; one associated with pneumonia, one with postmaturity, one with intracranial hemorrhage, and one in which cesarean section was performed for fetal distress—all four had autopsies). There was one case of placental insufficiency, with fetal distress and severe axphysia; an autopsy was performed. There was one case of cerebral and pulmonary edema with focal hemorrhage; autopsy was performed. There was one case of abruptio placentae with fetal distress (no autopsy). Thus, there was a chance for survival in only nine term babies born alive (i.e., corrected term fetal mortality rate of 0.3 in comparison to 0.5 per cent in the two earlier studies).

Fourteen of the 32 term babies were stillborn (six autopsies). In only two of the 14 was there any chance of fetal salvage by earlier cesarean section (i.e., one possible case of postmaturity and one with intermittent fetal distress).

Thus, it is encouraging that there has been some lessening of the fetal mortality rate. The reduction in total term fetal loss has been particularly significant.

Cesarean hysterectomy

There were 36 cesarean hysterectomies, an incidence of 1.4 per cent, with no deaths (Table VI). In one case the procedure was undoubtedly lifesaving. An 18-year-old, mentally retarded primiparous patient, with no antepartum care, severe pre-eclampsia, and neglected labor at *home* for several days, was admitted with a dead, macerated baby impossible to deliver vaginally. At cesarean section, marked peritonitis, amnionitis, purulent cystitis, and obstructive urinary retention was present, necessitating total hysterectomy and bilateral salpingo-oophorectomy; the long-standing pressure of a wedged fetal head resulted in necrosis avulsion of the bladder and rectum, leaving large vesicovaginal fistulas requiring diverting colostomy. There were permanent marked sequelae, although the patient survived. The morbidity rate was 33 per cent (only one case of severe morbidity). Sixty-nine per cent required blood transfusion (five single and 20 multiple). Of the 36, three were Wertheim procedures, 27 were total abdominal hysterectomies, and six were subtotal hysterectomies. The indications for hysterectomy are listed in Table VI.

Thus, almost one third of the cases were for sterilization. Transfusion was required in six of these cases; there was slight morbidity in two cases but no other complications. Admittedly, cesarean hysterectomy can be done for sterilization safely, as a rule, but there is always the definite possibility of increased risk and complications. Such cases should be selective, and ordinarily a gynecologic indication for hysterectomy should be present; otherwise, cesarean section with tubal ligation is still the method of choice for most operators. On the other hand, it must be realized that an individual, or group, may acquire the expertise through experience for safe performance with a minimum of complications.

Comment

Questionnaire returns from 50 representative medical school departmental chairmen, other professors, and selected individual obstetricians throughout the United States show that 10 years ago the average cesarean section rate ranged from 3 to 8 per cent, with the rate for the South Atlantic area being a little lower. Today the average rate is 9 to 12 per cent, with some in the 15 to 18 per cent range, the highest being 23 per cent. This is a dramatic increase. We have come a long way from the "conservative obstetrics" of the past. Again we should give credit to earlier colleagues who, years ago, advocated an increased cesarean section rate—D'Esopo in 1948, Dieckmann in 1950, and DeCosta in 1959. A change in attitude has occurred; formerly focus was on the mother and delivery, and now it is centered on fetal outcome.

Questionnaire statements.

Norman Thornton (University of Virginia) stated: "Obstetricians today are much more interested in the quality of the product they deliver than the cesarean section rate."

Charles Steer (Sloane Hospital for Women, New York City) remarked: "It is due to an increasing desire to spare the fetus any trouble whatever."

Graham G. Hawks (New York Hospital–Cornell Medical Center) said: "When one considers the marked increase in our section rate from 4.8 per cent in 1964 to 18.9 per cent in 1975 one is not struck by any marked change in the perinatal mortality but. . .by the change in infant morbidity (i.e., the absence of or greatly reduced obstetric trauma such as cerebral hemorrhage, convulsions, Erb's palsy, etc.)"

Elsie Carrington (Medical College of Pennsylvania) particularly stressed the number of "high-risk" patients now being found in medical centers. She stated that, based upon personal observations in traveling throughout the country, the rate has increased due to:

1. Liberalization of indications for section in terms of quality of life and *intact* survival in conditions known to be associated with trauma during vaginal delivery. This includes a marked reduction in vaginal deliveries for the term breech, also deep transverse arrest, and disappearance of version-extraction in singleton pregnancies.
2. More aggressive approach to the problem of premature rupture of membranes.
3. Use of section for acute herpesvirus Type 2 with intact membranes at the time the patient goes into labor.
4. The use of biochemical studies, ultrasonography, and electronic monitoring, which has worked both ways. It provides reassurance for vaginal delivery in some instances and permits selectivity of those that need to be delivered by cesarean section when fetal jeopardy can be substantiated.
5. The far more sophisticated intensive care facilities and personnel available for the management of the premature infant. These have permitted a common mutual decision to be made between obstetricians and neonatologists in connection with chronically distressed infants whom the neonatologist would prefer to have out of the uterus and salvageable—rather than be delivered in less favorable condition.

In this connection one should keep in mind the recent report of Bresnan,[9] a Harvard Medical School neurologist, about the small-for-date baby. He says that the large role played by truly intrauterine events as opposed to birth trauma is suggested by the strong association of brain damage with small-for-date infants as well as premature babies. He states that some studies, in which the children were followed for at least five years, showed that approximately one fourth had learning defects or other signs of cerebral dysfunction although neurological deficits which could be identified early in life were minimal. He further added that fetal brain damage can result from a variety of intrauterine events and may cause transitory or permanent neurological deficits whose cause may not be apparent at birth.

Charles Flowers (University of Alabama) stated: "We deliver all premature breeches by section and all term breeches, except the frank breech, by section unless the baby is about 'to fall out.'"

Leo Dunn (Medical College of Virginia) concurs in the decision to section the premature breech routinely.

Charles Hendricks (University of North Carolina) agrees with Flowers about the premature breech, then says: "Section unless there is an adequate pelvis and labor is fast and steady."

R. A. H. Kinch (Montreal General Hospital—McGill

University) says: "We almost routinely section primiparous breeches and any breech in which the legs are not extended." Kinch also adds: "To try and judge an obstetric unit by cesarean section rate is fallacious. The reason for the increased rate is valid, i.e., the insistence that all babies should be born with the least possible trauma."

Therefore, I might add, regardless of one's own experience with breech delivery and one's own philosophy, the future cesarean section rate for breech presentation is going to be high.

Hendricks further adds: "(a) Cesarean section is a less threat for the mother than before, with better anesthesia, availability of blood transfusion and antibiotics; (b) (there is) increased awareness that prolonged labor, difficult delivery, and malpresentation, including breech, are potentially traumatic situations which can be largely obviated by the use of cesarean section; (c) (there is) increased ability by the pediatricians to salvage small babies and the recognition that delivery by section offers such babies the optimal chance for survivorship at a high potential."

At the annual meeting of the American College of Obstetricians and Gynecologists in Boston, in May, 1975, it was pointed out by several speakers that, appropriately used, fetal monitoring should not increase the cesarean section rate but, inappropriately used, it certainly will.

Mason Andrews (Eastern Virginia Medical School) believes that fetal scalp blood studies, as an additional source of information, will compensate for "overreading" the monitor in some cases.

Kenneth Ryan (Boston Hospital for Women) says that fetal scalp blood sampling is used only when trouble is suggested by monitoring, and he believes that this is very necessary as monitoring alone may lead to some erroneous conclusions and can result in unnecesary section.

Edward H. Hon[10] (University of Southern California) says that during labor and delivery all fetuses are at risk. To quote: "Even continuous heart rate monitoring is not enough. It would be remarkable if a single biophysical measurement would give us all the answers. It's important to look at the fetal biochemistry or the acid-base status by taking blood sample from the fetal scalp."

Richard H. Paul (University of Southern California) says: "We do not use routine fetal scalp blood sampling (FBS) in patients being monitored but use it whenever we are dealing with confusing fetal heart rate patterns, or when there is need for further comment on fetal well-being in addition to monitoring. We utilize FBS in approximately 5 to 10 per cent of monitored patients. We feel there are patterns which are so well-defined as to dictate intervention without confirmation by biochemical data. We strongly feel that neither FBS nor monitoring is the final answer in fetal assessment. Monitoring is a primary tool which at times can be complemented by FBS information. FBS alone is totally inadequate as a surveillance method and, in fact, has numerous pitfalls to avoid. FBS is, in fact, impractical in most obstetric hospitals today. I think that with consolidation and emergence of larger obstetric services it is an adjunct tool which has merit."

Paul adds: "Finally, in a philosophical note, I feel we do intervene early in an attempt to avoid possible 'risk of fetal damage.' Many times, this is probably unnecessary as judged by newborn outcome. This intervention comes out of our inability to precisely judge how much 'stress' is needed to produce damage. We can't run the risk. A similar unwillingness to accept risk is seen in the case of cesarean section for breech presentation."

Edward Quilligan[11] (University of Southern California) expressed it well when he said: "An alert obstetrician who is looking for complications, but hopefully not causing them, can use present-day obstetric techniques to help assure for the fetus a significantly safer journey through the antepartum and intrapartum periods—he can prevent that fetus from going from stress to distress."

Other reasons stated for an increased cesarean section rate by those who replied include a higher incidence of primigravidas and also older primigravidas.

Almost all replies to the questionnaire mentioned malpractice suits. Undoubtedly this is a factor in the increased cesarean section rate everywhere. In 1938, when this Association was founded, no one would have ever thought the malpractice threat would become an indication for cesarean section.

Medically, and legally, we are living in a different era—exciting but extremely hazardous. Incidentally, how does one practice "defensive obstetrics" without losing the all-important doctor-patient relationship, which makes it all so worthwhile?

Cesarean section rate of the future

What about the cesarean section rate of the future? Such prediction is always subject to error, admittedly, but one can study the trend. On the basis of our experience at Charlotte Memorial Hospital, plus the majority of questionnaire returns, it would appear that a rate of 10 to 15 per cent will be the average, depending, of course, upon the type of patient census of the individual hospital. Questionnaire opinions varied, as would be expected:

Anthony D'Esopo (Sloane Hospital, New York City),

now several years retired, said that in his private practice he was able to get by with a 10 per cent rate without regrets.

R. Gordon Douglas (fomerly of New York Hospital, but now retired, and a consultant at Women and Infants Hospital of Rhode Island) said: "You ask the impossible question. Certainly when the prevalent rate was 1 to 3 per cent that was too low. I would consider 20 per cent too high. Maybe somewhere in the range of 8 to 10 per cent would be optimum. If the rate of cesarean section does not lower perinatal deaths and morbidity, it will be difficult to justify continuation of the practice."

Predictions of 8 to 10 per cent were also expressed by Queenan (University of Louisville), Andrews, and Ingram (University of South Florida). Decker (Mayo Clinic), whose present rate is 7.8 per cent, believes that it will rise to 10 per cent because of high-risk cases.

W. C. Keettel (University of Iowa) replied: "Our present rate is 9.9 per cent. It would be my impression that the rate will continue to rise as I think we are developing a generation of physicians who are not familiar with the use of forceps or the art of breech delivery, and more and more potential complications will be managed by cesarean section."

The same thought was expressed by others too.

Quilligan (University of Southern California), Kinch, and Pearson (Indiana—Purdue University) quoted: "10 to 12 per cent." However, Pearson stated: "We haven't seen any continued remarkable decrease in perinatal rates after the 8 to 9 per cent rate was reached, and there is evidence that the maternal mortality and morbidity rates are being affected adversely."

Gordon W. Douglas (New York University) said: "I doubt if there is such a thing as a 'proper' section rate. At one time the onus was on the obstetrician to document absolute need for abdominal intervention, and a low rate was equated with obstetric expertise. In these days the focus is on a bad outcome, and since section with appropriate anesthesia and support systems is so safe, the maxim 'better safe than sorry' has taken a new meaning. In the absence of startling new concepts leading to increased intervention, I think a range of 12 to 15 per cent is appropriate for a teaching referral service, although this would be high for the obstetrician in community practice."

Those predicting the 10 to 15 per cent range include Greene (University of Kentucky), Thornton, Mickal (Louisiana State University), Scoggin (Medical College of Georgia), Tovell (St. Luke's Hospital, New York City), Flowers, Carrington, Hendricks, Holzaepfel (Ohio State University), and Dunn.

Tommy Evans (Wayne State University), whose present rate is 11.5 per cent, said: "Obviously a high section rate does not necessarily mean good or bad obstetric care. I suspect that our rate will rise to 12 to 15 per cent in the next few years, primarily because we deal with an ultra high-risk population."

Crenshaw (Duke University) and Granados (University of Maryland) quoted: "12 to 14 per cent."

Ryan, whose present rate is 18 per cent, believes it will probably decrease to 14 to 15 per cent.

Frank C. Greiss, Jr. (Bowman Gray—Wake Forest University) stated: "With respect to the future section rate, I believe that this will settle out after increased experience with a more liberal section rate into a satisfactory compromise between an aggressive concern for fetal well-being, and the conservative application of tried and true methods. This rate will probably fall somewhere around 15 per cent."

Long (Emory University) agrees with a 15 per cent rate; Gabert (University of Utah) and Hester (Medical University of South Carolina) concur with a 15 to 17 per cent rate.

Weingold (George Washington University) thinks an 18 to 20 per cent rate is probable, as does Steer.

Morton (Kaiser-Permanente Hospital, Los Angeles) says 20 per cent as do Fuchs, Benson (University of Oregon), and Krantz (University of Kansas).

Spellacy (University of Florida) thinks there will be 15 to 25 per cent, and Barter (George Washington University) quoted 20 to 25 per cent.

The prediction of the private obstetricians ranged from 8 to 15 per cent, with the average being 10 per cent.

Thus, there is considerable variation in the predicted cesarean section rate of the future, just as there is in the present rate. Full and logical explanations have been given by many outstanding departmental chairmen, professors, and private obstetricians throughout the country. Personally, I can see it from the point of view of the private obstetrician, the community hospital, and the high-risk medical center. As long as the decision for cesarean section is made in the best interest of all concerned, there can be no real fault. Adequate training, obstetric knowledge, experience, and research, together with careful review of outcome, should result in the proper use of cesarean section.

In conclusion, therefore, I would like to say that during my professional career of 40 years, cesarean section has changed from an operation of necessity to an operation of choice, with better maternal results and certainly with better fetal results. Indeed, we have come a long way.

REFERENCES

1. Jones, O. H.: The trend in cesarean section in recent years, AM. J. OBSTET. GYNECOL. **66:** 765, 1953.
2. Jones, O. H.: Trends in the incidence of and indications for cesarean section at Charlotte Memorial Hospital during the last 10 years, AM. J. OBSTET. GYNECOL. **87:** 319, 1963.
3. Douglas, R. G.: Discussion of Jones,[2] page 318.
4. Douglas, R. G.: Discussion of Jones,[1, 2] page 765 and page 319.
5. Fisher, D. E., and Paton, J. B.: The effects of maternal anesthetic and analgesic drugs on the fetus and newborn, Clin. Obstet. Gynecol. **17:** 278, 1974.
6. Ranney, B.: Advantages of local anesthesia for cesarean section, Obstet. Gynecol. **45:** 163, 1975.
7. Brown, W. U., Jr., Bell, G. C., and Alper, M. H.: Acidosis, local anesthetics, and the newborn, Obstet. Gynecol. **48:** 27, 1976.
8. Scanlon, J. W., Shea, E., and Alper, M. H.: Personal communication.
9. Bresnan, M. J.: Presented at the First Memorial Ignatz Semmelweis Seminar at the New Jersey Medical School, Newark, New Jersey, 1975.
10. Hon, E. H. G. (Guest Editor), Dr./3 Perinatal Medicine: Dr. to Dr.: How to Identify the High-Risk Fetus, Prepared by Medcom, Inc., 2 Hammarskjold Plaza, New York, New York 10017, for Wyeth Labs., Div. American Home Products Corp., P. O. Box 8299, Philadelphia, Pennsylvania 19101, 1975, p. 23.
11. Quilligan, E. J. (Moderator), Dr./3 Perinatal Medicine: Dr. to Dr.: How to Identify the High-Risk Fetus: Roundtable of University of Southern California Perinatologists, Prepared by Medcom, Inc., 2 Hammarskjold Plaza, New York, New York 10017 for Wyeth Labs., Div. American Home Products Corp., P. O. Box 8299, Philadelphia, Pennsylvania 19101, 1975, p. 24.

Accurate amniotic fluid bilirubin analysis from the "bloody tap"

A preliminary report

CHARLES J. HOCHBERG, M.D.
ALAN P. WITHEILER, PH.D.
HELEN COOK, M.T.-ASCP
Tampa, Florida

The quantitation of bilirubin in amniotic fluid is of paramount importance in prognosticating the severity of Rh isoimmunization. Amniotic fluid contaminated by maternal blood can result in erroneous results when direct spectrophotemetric analysis is performed on such fluid. The technique and results of a one-step chloroform extraction performed on "bloody" amniotic fluid is presented. Results confirm that chloroform extraction yields more accurate clinical information in regard to Rh isoimmunized patients in whom a "bloody tap" is obtained. (AM. J. OBSTET. GYNECOL. 126: 531, 1976.)

SINCE THE original observation by Bevis[1] that bilirubin pigments in amniotic fluid (AF) have optical densities near 450 mμ, several methods have been developed for analyzing AF bilirubin to aid in the management of rhesus factor isoimmunization. Liley,[2, 3] Whitfield,[4] Freda,[5] and others[6] have plotted the change in optical density at 450 mμ, derived by subtracting the actual absorbance from the theoretical absorbance, against the weeks of gestation.

Because accurate readings of the ΔO.D. at 450 mμ is of major prognostic importance, it is often distressing to obtain "contaminated" or "bloody" AF at the time of amniocentesis. AF containing maternal blood or containing oxyhemoglobin methemoglobin, or methamalbumin may be difficult or impossible to read with any confidence at 450 mμ. Frequently, following a "bloody tap," these pigments will persist within the AF for days or weeks, so that subsequent fluid specimens will still produce a distorted curve on spectrophotometric analysis and produce an unreliable reading at 450 mμ.

In 1969, Brazie and associates[7] presented a method of extracting bilirubin with a buffered chloroform solution. In 1970, Mallikarjuneswara and associates[8] reported a method of extracting unconjugated bilirubin from AF with the use of aniline in chloroform (1 ml. per 100 ml.). Thus, in spite of contaminating pigments, a true ΔO.D. at 450 mμ was obtained.

In a search for a simpler and more useful method for clinical use, a one-step chloroform extraction technique was devised by the essayist.

The objectives of this presentation are (1) to determine if the simpler technique is an accurate laboratory procedure and (2) to evaluate the clinical usefulness of this method in a small series of patients.

Materials and methods

Study 1. Unconjugated bilirubin, 0.1 ml. (20 mg. per 100 ml.), was added to 3 ml. aliquots of six separate uncontaminated AF specimens. The fluid was then scanned on a Coleman-124 spectrophotometer to trace a continuous curve of optical density on linear paper between 350 and 700 mμ.

Then 3 ml. of chloroform were added to the specimen; the resultive mixture was shaken for 30 seconds on a Vortex mixer and centrifuged for 5

From the Department of Obstetrics and Gynecology, College of Medicine, University of South Florida, and Tampa General Hospital.

Foundation Prize Thesis presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. Charles Hochberg, Department of Obstetrics and Gynecology, University of South Florida, Tampa, Florida 33620.

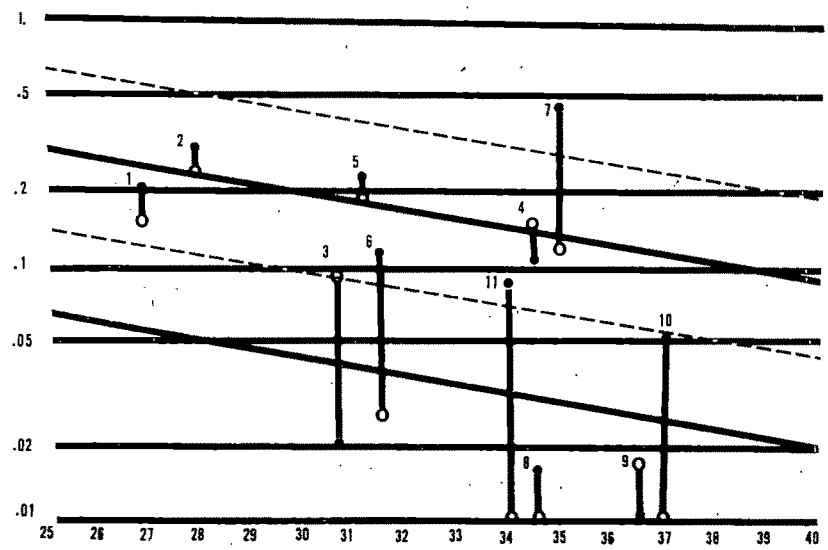


Fig. 1. Eleven cases where direct spectrophotometric analysis differed from chloroform analysis—charted on Liley prognosis graph. • = Bilirubin—direct spectrophomatic analysis; o = Bilirubin—chloroform extraction.

Table I. Bilirubin values by direct spectrophotometry, chloroform extraction, and chloroform extraction with blood added

Exp. no.	*Direct spectrophotometry: ΔO.D. 450 mμ*	*Chloroform extraction: ΔO.D. 450 mμ*	*Chloroform extraction: ΔO.D. 450 mμ (blood added)*
1	0.10	0.10	0.09
2	0.08	0.08	0.08
3	0.09	0.08	0.09
4	0.07	0.07	0.07
5	0.07	0.07	0.07
6	0.10	0.10	0.09

minutes at 3,000 r.p.m., after which the chloroform layer was removed by pipet. The sample was scanned as above, blanking the spectrophotometer with chloroform.

To a second matched 3 ml. aliquot of AF with the same quantity of bilirubin, 0.15 ml. of maternal red blood cells was added. Then 3 ml. of chloroform were added and a similar extraction was carried out.

Study 2. All patients with Rh-sensitized pregnancies seen in our department from August, 1972, through August, 1975, were evaluated by amniocentesis. Sixty samples of AF were obtained from 26 patients between weeks 24 and 40 of gestation by percutaneous abdominal punctures. Twenty-one of these samples were "bloody taps." The method described by Liley was used in all samples to determine the quantity of bilirubin at an optical density at 450 mμ and plotted against the weeks of gestation. The "bloody tap" specimens were analyzed by the standard method of Liley, and also by the chloroform method described above, and values were plotted on the Liley curve.

Results

Study 1. The recovery of added bilirubin in the two aliquots of each specimen is shown in Table I. When comparing direct spectrophotometry to the chloroform method, no differences in the values are obtained, thus demonstrating that all added bilirubin is extracted by chloroform.

The presence of blood in samples of AF did not interfere with the quantitative determination of bilirubin when blood pigments were extracted by the chloroform method (Table I).

Study 2. Of the 21 "bloody taps" obtained, 11 analyses demonstrated a significant difference between the direct spectrophotometry method and the chloroform extraction method. Significant difference is defined as a variation of greater than 0.01 at 450 mμ (Table II). Of the remaining ten "bloody taps," there was no significant difference between the direct spectrophotometric analysis and the chloroform extraction analysis.

The 11 cases are plotted on a Liley chart for prognosis in erythroblastosis fetalis (Fig. 1).

In six patients there was a major difference between the values obtained by direct spectrophotometric analysis and the chloroform extraction method. The fetal outcome was accurately predicted in all cases by the chloroform extraction method (Table III).

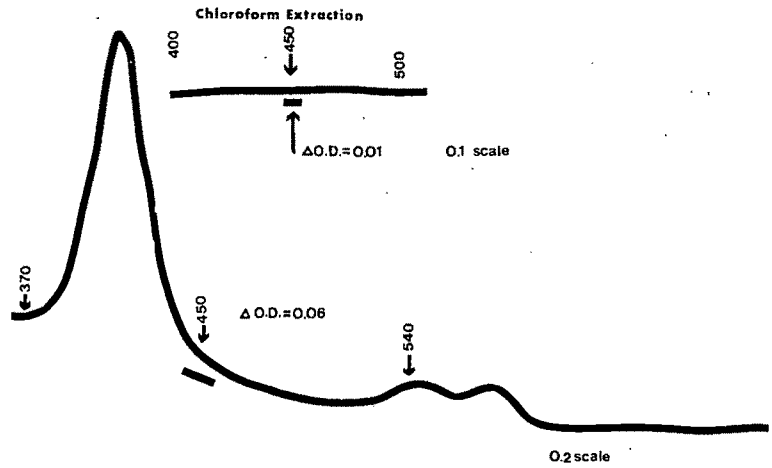


Fig. 2. Direct spectrophotometric analysis compared to chloroform extraction.

Table II. Cases in which there was significant difference between direct spectrophotometry and chloroform extraction

Case no.	*Gest. age (wk.)*	*Direct spectrophotometry: ΔO.D. 450 mμ*	*Chloroform extraction: ΔO.D. 450 mμ*	**Liley zone changes*
1	27	0.2	0.17	m/s → m/s
2	20½	0.32	0.30	s → s
3	30½	0.04	0.09	u/m → m/s
4	34	0.12	0.15	m/s → s
5	31	0.24	0.21	u/m → u/m
6	31½	0.13	0.03	m/s → u/m
7	35	0.44	0.13	vs → m/s
8	34½	0.03	0.01	u/m → u/m
9	36½	0.01	0.25	u/m → u/m
10	37	0.06	0.01	m/m → u/m
11	34	0.09	0.01	m/s → u/m

*vs = very severe, s = severe, m/s = moderate/severe, m/m = mild/moderate, and u/m = unaffected/mild.

Table III. Cases in which major differences existed between the direct and chloroform and the fetal outcome*

Case No.	*Direct spectrophotometry: ΔO.D. 450 mμ*	*Spectrophotometric analysis after chloroform extraction: ΔO.D. 450mμ*	*Outcome*
3	0.04 (u/m)	0.09 (m/s)	Stillborn, 35 wk.
4	0.12 (m/s)	0.15 (s)	Delivered, 34 wk.; 3 double vol. exchanges/lived
6	0.13 (m/s)	0.03 (u/m)	Stillborn, mult. cong. anom.
7	0.44 (vs)	0.13 (m/s)	Delivered, 35 wk.; 4 double vol. exchanges/lived
10	0.06 (m/m)	0.01 (u/m)	Rh+, Coombs+; no exchanges/lived
11	0.09 (m/s)	0.01 (u/m)	Rh− Coombs−/lived

*Numbers correspond to Table II.

Comment

Although the incidence of "blood taps" has decreased with the use of sonography, such taps are still not an unusual occurrence. In these patients, the problem of determining bilirubin levels accurately for clinical management persists.

If bloody fluid distorts the ΔO.D. at 450 mμ, it is often impossible to quantitate bilirubin accurately. The wide difference in values in one patient is seen in Fig. 2. The ΔO.D. at 450 mμ with direct spectrophotometric analysis is 0.06 (in the moderately affected/-slightly affected zone) on the Liley chart. However, with chloroform extraction the ΔO.D. at 450 mμ is 0.01 (in the unaffected/slightly affected zone). The baby delivered by this patient was Rh positive and Coombs positive, but required no therapy.

Chloroform extraction may also result in a higher amount of bilirubin. As seen in Fig. 3, the bilirubin

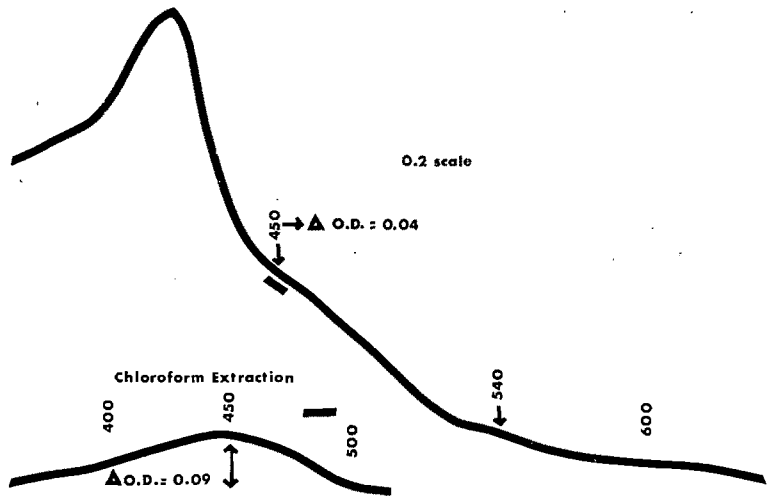


Fig. 3. Direct spectrophotometric analysis compared to chloroform extraction.

concentration by the chloroform method is 0.09 (in the moderate/severe range) on the Liley chart. By direct spectrophotometric analysis the ΔO.D. at 450 mμ is 0.04 (in the unaffected/mildly affected range). This pregnancy ended in the delivery of a stillborn infant at 35 weeks of gestation.

In this small series of patients, chloroform extraction resulted in both an increase and decrease in bilirubin values, when compared to the distorted curves from the direct spectrophotometric analyses. This distortion appears to be evident in approximately 50 per cent of the analyses of "bloody taps"; the remaining analyses show no difference at 450 mμ between direct spectrophotometry and chloroform extraction. Regardless of the direction of shift, chloroform extraction provided more accurate prediction of the fetal outcome when dealing with bloody amniotic fluid. Since there is no way of determining which "bloody tap" is affecting the spectrophotometric curve at 450 mμ, it is recommended that when dealing with a "bloody tap," as demonstrated by peaks at 410 to 420 mμ, a chloroform extraction should be performed.

REFERENCES

1. Bevis, B. C. A.: Blood pigments in hemolytic disease of the newborn, J. Obstet. Gynecol. Br. Emp. **64:** 68, 1956.
2. Liley, A. S.: Liquor amnii analysis in the management of the pregnancy complicated by rhesus sensitization, AM. J. OBSTET. GYNECOL. **82:** 1359, 1961.
3. Liley, A. S.: Errors in the assessment of hemolytic disease from amniotic fluid, AM. J. OBSTET. GYNECOL. **86:** 485, 1963.
4. Whitfield, C. R.: A three year assessment of an action line method of timing intervention in rhesus isoimmunization, AM. J. OBSTET. GYNECOL. **108:** 1239, 1970.
5. Freda, V. J.: The Rh problem in obstetrics and a new concept of its management using amniocentesis and spectrophotometric scanning of amniotic fluid, AM. J. OBSTET. GYNECOL. **92:** 341, 1965.
6. Robinson, J. G.: Management of patients with Rh isoimmunization based on amniotic fluid examination, AM. J. OBSTET. GYNECOL. **103:** 713, 1969.
7. Brazie, J. V., Bowes, W. A., Jr., and Ibbott, F. A.: An improved, rapid procedure for the determination of amniotic fluid bilirubin and its use in the prediction of the course of Rh-sensitized pregnancies, AM. J. OBSTET. GYNECOL. **104:** 80, 1969.
8. Mallikarjuneswara, V. R., Clemetson, C. A. B., and Carr, J. J.: Determination of bilirubin in amniotic fluid, Clin. Chem. **16:** 180, 1970.

The individual at high risk for endometrial carcinoma

SAUL B. GUSBERG, M.D.

New York, New York

Epidemiologic studies can help us recognize high-risk factors in endometrial carcinoma. The definition of high-risk factors, especially at the menopause, can lead to prophylactic measures that may aid in the control of this disease. This recognition of the high-risk patient in the perimenopausal years may be aided by aspiration curettage of ambulatory women, for such a strategy of surveillance is practical and efficient. Increasing acceptance of hormone sensitivity in neoplastic abnormality of the endometrium can also influence us in identifying the patient at risk. (AM. J. OBSTET. GYNECOL. 126: 535, 1976.)

I AM PRIVILEGED to be your guest at this 1976 meeting of the South Atlantic Association and honored to have the opportunity to present to you some data concerning the high-risk patient for your consideration.

Indeed, I presented some of this material in England where I was less anxious, for I was informed that the English instinctively admire Americans with little talent, provided that they are modest about it.

My long-time interest in endometrial cancer arose because this tumor, arising in a hormone-sensitive tissue, seemed to offer a possible link between the dysfunctional and the neoplastic, an answer to the endocrine-tumor problem. I can guess that you do not expect me to present the etiology of endometrial carcinoma today, yet the identification of the high-risk patient can lead to control in a manner similar to that we have witnessed for cervical cancer. In fact, in the past two decades, it is probable that advances in early detection have done more to control cancer than have advances in treatment.

As a clinician, I am somewhat timid about presenting epidemiologic and hormonal data, but personal study in some of the geographic areas which I shall describe and the generous collaboration of my gifted steroid colleagues have encouraged me in these diversions.

From the Department of Obstetrics and Gynecology of The Mount Sinai School of Medicine and The Mount Sinai Hospital.

Supported in part by Special Appropriation from the American Cancer Society.

Presented as Guest Speaker at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. Saul B. Gusberg, Department of Obstetrics and Gynecology, Mount Sinai School of Medicine, Fifth Ave. and 100th St., New York, New York 10029.

Environmental factors

The studies of Christopherson and his colleagues,[1] the age-specific Birmingham data of Taylor,[2] those of the states of Connecticut and California,[3] and that of Norway indicate a significant rise in the incidence of endometrial carcinoma. While the last national cancer survey in our country denies this rise,[4] it does not take into account several factors, including the increased incidence of hysterectomy. It is alleged by some that the increasing life expectancy of women and the control of cervical cancer have emphasized endometrial cancer. In fact, there is little doubt that this disease is becoming the predominant uterine cancer in industrialized countries. It is clear that there is a disparity between its incidence in rich and poor in our country and this has a geographic counterpart in developing countries, for the incidence in Asia, Africa, and South America is very low compared to that in North America and Europe.[5] In the United States of America, the age-adjusted rate in whites is 20.1 compared to that for blacks, which is 9.3—more than twice as high in the generally more affluent group.

It is well known that Asian women generally have a low incidence of endometrial and breast cancer, but one must be careful of characterizing a distant population as homogeneous. For example, the very high rate of stomach cancer in Japan seems to be reduced as one moves southward in the Japanese islands,[6] whereas the prevalence rate of nasopharyngeal cancer in Chinese, very high in any case, increases as one moves from north to south.[7, 8] Furthermore, migrant studies are very interesting for they indicate that Japanese moving to Hawaii and California show a distinct change in tumor incidence especially noted in the Nisei and

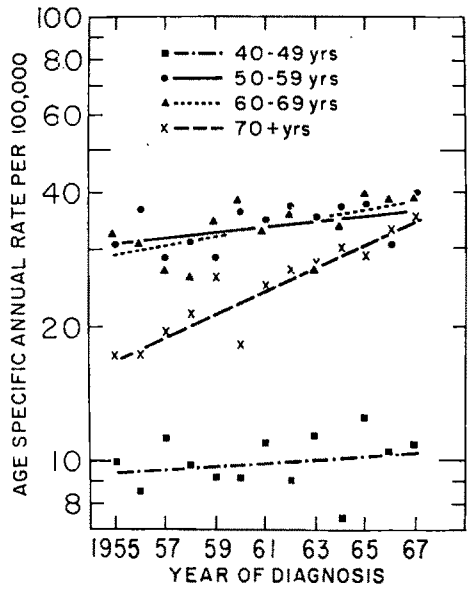


Fig. 1. Incidence of cancer of the uterine corpus in Norway.

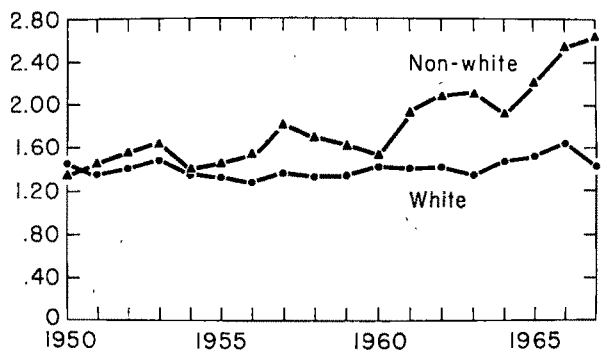


Fig. 2. Corpus cancer mortality rate, United States of America. (From Cancer Mortality U.S.A., N.C.I. Monograph, 1971.)

Sansei (first and second American born generations). Their rate of stomach cancer decreases, the rate of colon cancer increases, as does the rate of endometrial and breast disease more modestly,[9] the latter especially during the child-bearing period.[10] It may be appropriate to the endometrial problem to note that the rate of latent prostate cancer in Japanese, in Japan and in Hawaii, is similar, while the rate of invasive prostate cancer, very low in Japan, rises in Hawaiian Japanese toward Caucasion high levels. This suggests a growth-promoting factor in the Western environment for this tumor.[11]

As you know, the ethnicity in Hawaii is especially suitable for cancer epidemiologic studies for the population is composed of approximately one third Caucasian, one third Japanese, and one third Chinese, Hawaiians, and Filipinos. An excellent tumor registry aids the study of these individuals in this island population which is noteworthy for persons of Oriental origin living in a "Western" environment.

One gains the impression of an internal migrant phenomenon in an analysis of the mortality rate for endometrial cancer in the population studies of our country. The rate for whites has remained steady since 1950, whereas the rate for blacks appears to have risen significantly.[12] This time period coincides with the steady migration of the southern rural Negro to improved economic circumstances in the industrialized cities of the north. It may also be of interest that Masubuchi[13] has reported an increase in endometrial carcinoma in Tokyo as the Japanese have adopted a Western-type, high-protein, high-animal-fat diet. One must also note that in Manila, in the Philippines, a very "westernized" Oriental city, the risk for breast and endometrial cancer appeared notably higher than that in other Asian cities.[14] In another geographic area one sees a similar phenomenon for, in a study of the prevalence of cervix and endometrial cancer in Israel,[15] it was shown that Israelis of European origin have a Western pattern with a high corpus and breast[16] incidence and a very low cervix cancer incidence whereas those individuals of African origin have a so-called "Oriental" mode with a converse distribution.

Surely, these geographic differences must represent predominance of environmental factors over genetic ones and, indeed, they lead one to speculation that such factors, with special reference to the high-animal-fat "Western" diet, may play a role in the development of endometrial carcinoma.[17] We do know that nutritional factors can impinge on the endocrine system, for all gynecologists have seen amenorrhea and failure of ovulation occur with striking weight gain or weight loss (Fig. 1 illustrates such a possible mechanism).

Hormone sensitivity

It is surely unnecessary for me to review the endocrine stigmas that place some at high risk for endometrial cancer. Suffice it to say that the evidence for hormone sensitivity provided by some clinical observations is very strong: (1) obesity, (2) infertility, (3) coincidence of functioning ovarian tumors, (4) coincidence of the cystic ovarian syndrome and failure of ovulation, (5) dysfunctional bleeding, (6) diabetic diathesis, (7) progestational effect on metastatic disease, (8) development of endometrial carcinoma in young women treated with estrogen for ovarian agenesis, (9) induction of adenomatous hyperplasia and carcinoma with exogenous estrogens, and (10) estrogens as immunosuppressants.[18]

The risk for endometrial carcinoma in large and obese women has been known for many years[19] and studied with more precise epidemiologic methods recently to reveal that women[20] who are 21 to 50 pounds over average weight have a threefold greater risk, whereas those 51 pounds or more over average weight have a ninefold greater risk. Those with increased height also were at greater risk, even independent of obesity. A recent Boston study[21] also confirmed nulliparity to produce a twofold risk over that of those with one child and a threefold risk over that of those with five children; in addition, diabetic subjects incurred a 2.8-times risk and those in the menopause, beyond age 52, a 2.4-fold risk—even those whose cancer occurred in the 60 to 69 year or over 70 age groups.

The modern era of steroid metabolic technology has offered us new evidence of the hormone sensitivity of cancer in target organs. Since breast and endometrial cancer tend to correlate in the same kinds of populations,[22] it may be of interest to note the studies reported by Brown in 1958, wherein administered estradiol was excreted as estriol in greater ratio by those with breast cancer than by control subjects.[23] Excretion studies in breast cancer have been the subject of much interest since that time; recently MacMahon and colleagues[24] have suggested a screening mechanism by their demonstration that in a group of young Asian women, 15 to 19 years of age, destined to have a low rate of breast and endometrial cancer compared to Caucasians, there was a higher ratio of estriol over estrone and estradiol in the urine. Studies by our group[25] also show that postmenopausal women with endometrial carcinoma tend to excrete less total estriol as compared to estrone than do normal women in the same age group. This interests us, for studies in our laboratories have demonstrated that estriol competes for the estradiol-binding site.[51]

MacDonald, Gordin, and Siiteri[26] have demonstrated that the adrenal precursor Δ4-androstenedione is undoubtedly the estrogen prehormone in postmenopausal women and their group and Longcope[27] reported double the conversion rate of androstenedione to estrone in this age group as compared to cycling women. They also noted that postmenopausal bleeders have a higher conversion rate than control subjects and since that time, our group[28] and theirs[29] have demonstrated that postmenopausal women with endometrial cancer have a significantly higher conversion rate to estrone than do control subjects. Rubin and associates[30] in our laboratory have also shown that the ratio of estrone to estradiol in plasma is higher in those women with endometrial carcinoma.

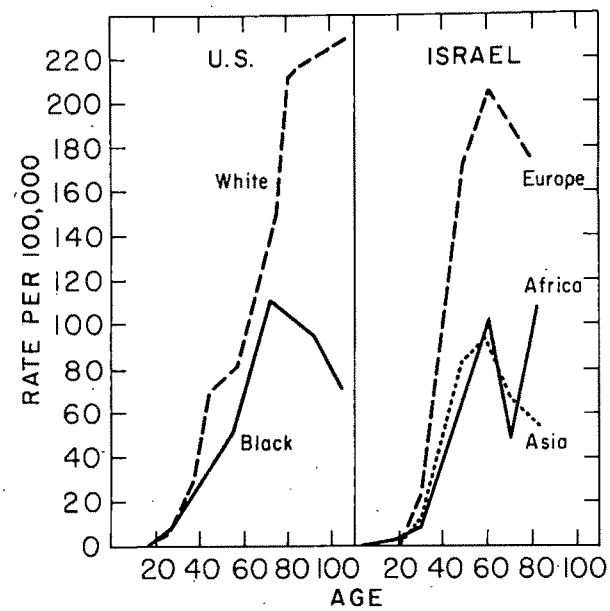


Fig. 3. Interethnic comparison of mean annual incidence of breast cancer in Israel and the United States. (After Modan: Israel J. Med. Sci. 10: 1112, 1974.)

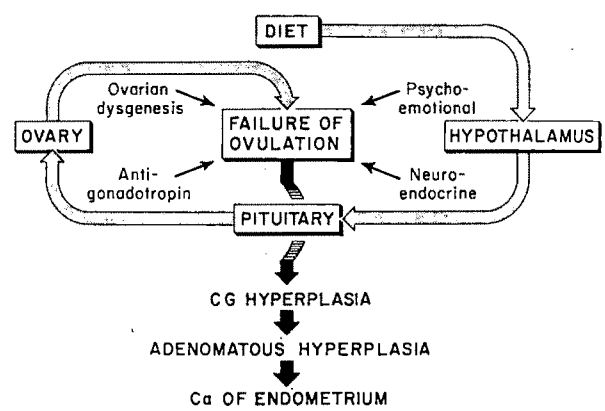


Fig. 4. Cancer of the endometrium. (After Gusberg, S. B.: Proc. R. Soc. Med. 68: 163, 1975.)

With androstenedione as a prehormone and estrone the postmenopausal estrogen, it would appear that aging, obese women with endometrial cancer have a significant production rate of estrone. In fact, MacDonald and associates[29] have suggested that women at high risk for endometrial carcinoma either have a high plasma androstenedione (cystic ovarian syndrome with infertility or ovarian stromal hyperplasia) or have an increased conversion rate to estrone (aging and obesity). In fact, their studies show a 15- to 20-fold increase in conversion in markedly obese older women compared to their young, slender counterparts. Twombley and his colleagues,[31] in a study after injection of

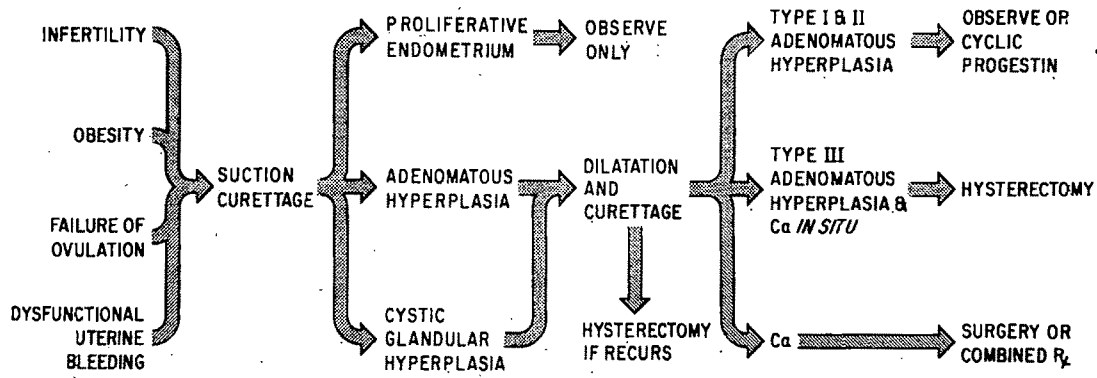


Fig. 5. Management of the high-risk menopausal patient.

Table I. Carcinoma incidence in five continents, age standardized*

	Columbia, Cali.	*U.K., S.W.*	*Japan*	*U. S. A., Conn.*	*Israel*	
					Born Europe	*Born Africa or Asia*
Cervix	75.6	13.6	20.6	10.3	4.2	6.7
Corpus	6.8	10.2	1.3	15.3	10.7	4.5
Breast	27.3	50.6	11.0	62.3	55.5	22.2
Prostate	23.2	21.7	3.2	33.0	11.4	13.2
Stomach (F)	24.8	11.2	44.7	6.8	11.1	17.9

*After Doll et al: U.I.C.C. Report, Vol. 2, 1970.

^{14}C-labeled estradiol, showed less excretion in obese than lean subjects and speculated that estrogen could be stored in fat and gradually escape, giving chronic stimulation. Schindler and his colleagues[32] have reported a threefold increased conversion rate in fat in vitro from patients with endometrial cancer over those with benign disease, though they did not give the weight or age of their patients.

The early work of Jensen[33] opened the field of steroid receptor sites in hormone-sensitive tumor areas. Brush, Taylor, and King[34] reported that several endometrial cancers showed estradiol uptake and since that time, their group[35] and ours have shown estradiol receptors in significant numbers of aging patients with endometrial cancer. Rubin and associates[30] in our laboratories studied these tumors systematically and we have demonstrated specific estradiol receptors in 32 per cent of the tumors without age correlation or relation to differentiation. Terenius and his collaborators[36] and McGuire and Julian[37] have also shown specific estradiol binding and the Jenson group claimed this specific binding to be hormone dependent. Indeed, Jensen and his colleagues,[38] in a study of human breast cancer, reported that only one of 29 with negative estradiol receptors responded to adrenalectomy, whereas 10 of 13 responded who had demonstrable receptors. Progesterone receptor site technology still requires further development and its relationship to the high-risk patient remained investigational.

No one would fail to notice that tumors and hormone-sensitive tissues such as breast, endometrium, and prostate peak at a time of life when these organs are involuting or atrophic. It would appear from the above studies of alternative sites of secretion of prehormone, the receptivity of the aging tissues, and the extraglandular capacity for aromatization, that one cannot discount steroid stimulation of these otherwise involuting organs.

Our own interest in identification of high-risk patients was reported first in 1947[39] and again in 1954,[40] with the description in our first report of adenomatous hyperplasia as a cancer precursor and the relation of this precursor and adenocarcinoma to endogenous and exogenous estrogen.

In 1961 we reported a group of endometrial carcinomas that appeared to be estrogenically conditioned.[41]

In 1963 we identified a group of patients with adenomatous hyperplasia as a high-risk group with a prospective study.[42]

In 1971[43] we reported a group of patients harboring theca- or granulosa-cell tumors in the postmenopausal era that had provoked adenomatous hyperplasia or carcinoma.

Since that time we have reported receptor-site

Table II. Uterine cancer in Bangkok: Registered cases

	Siriraj, 1971	*Chulalongkorn, 1972*
Cervix	389	204
Corpus	24	22

Table III. Hong Kong cancer registry: New cases registered*

	1965	*1966*	*1967*	*1968*	*1969*	*1970*
G.I. (F.)	508	375	393	405	503	352
Breast	389	312	335	361	360	318
Cervix	824	535	479	440	545	441
Corpus	76	108	69	70	111	72

*After H. C. Ho.

studies of hormone sensitivity as above described and the steroid metabolism in those with endometrial carcinoma.

As is now well known, within recent weeks, reports from California and Seattle indicate a 4.5- to 7.6-fold increase in the incidence of endometrial carcinoma in association with administered estrogen over age-matched controls.[3, 44]

Identification by histologic screening

It seems logical to conclude that control of this disease by knowledge of high-risk factors must include the definition of cancer precursors and the possibility of their interruption. It has become commonplace to consider the syndrome of obesity, infertility, failure of ovulation, and dysfunctional bleeding of the menopause as placing subjects at high risk for adenomatous hyperplasia and endometrial carcinoma.

The history of this developmental concept may be abstracted as follows:[39, 42, 45]

1900—*Cullen* describes atypical hyperplastic change as a sign of cancer nearby.

1923 *Robert Meyer* reports conversion of hyperplasia to carcinoma in several patients.

1932 *Howard Taylor* emphasizes the significance of postmenopausal hyperplasia.

1936 *Novak and Yui* make the same emphasis.

1947 *Gusberg* names and defines adenomatous hyperplasia as *the* endometrial cancer precursor.

1948 *Novak and Rutledge* affirm the distinction from cystic glandular hyperplasia and carcinoma.

1949 *Hertig and Sommers* confirm this concept and separate carcinoma in situ.

Of course, many others have made contributions to this knowledge since that time and a recent survey of

Table IV. Age-standardized incidence rate for cancer in Japanese women*

Residence area	*Years*	*Incidence rate for cancer of the*				
		Breast	*Ovary*	*Corpus*	*Cervix*	*Stomach (F)*
Okinawa	1968	5.7	1.8	0.3	46.5	22.8
Osaka	1965-66	10.4	2.7	1.0	17.9	48.4
Miyagi	1962-64	10.8	1.9	1.3	20.6	44.7
Okayama	1966	11.9	2.7	2.0	21.9	45.4
Hawaii	1960-64	23.0	9.4	10.8	14.6	26.9
(Caucasian in Hawaii)	1960-64	62.9	14.8	17.5	15.4	8.8

*From Dr. T. Hirayama, Chief Epidemiology, Nat'l. Cancer Center, Tokyo.

Table V. Nasopharyngeal cancer in Hong Kong*

Origin	*Age-standardized rate per 100,000*
Hong Kong†	15.8
Canton and Macao	12.7
Sz Yap	14.2
Chiu Chou	8.0
Kwangtung	8.0
Central coastal province	4.0

*After H. C. Ho, U.I.C.C., Monograph 1.10.

†"Boat people" in Hong Kong almost twice as high as others.

Table VI. Cancer risk change for Japanese females migrant to U. S. A.*

Standardized mortality rates, Japan = 100	*Japanese*	*Japanese migrants to U.S.A.*	*U.S.A.–born Japanese*	*U.S.A. white*
Stomach	100	55	48	18
Colon	100	218	209	483
Breast	100	166	136	591
Ovary	100	337	—	535
Cervix	100	52	33	48
Corpus†	100	209	—	330

*From Haenszel and Kurihara: J. Nat'l Cancer Inst. 40: 43, 1968.

†Japanese figures include chorioca, U.S.A. do not.

prospective studies with relatively short follow-up showed an 18.5 per cent progression[46] from adenomatous hyperplasia to carcinoma in a combined series of 562 patients, excluding those lost to follow-up or treated immediately by hysterectomy. In our series a cumulative risk of 30 per cent at 10 years was demonstrated over controls.[42]

I have reviewed elsewhere definitions of these precursors,[47] for semantic variations have been counterproductive. Adenomatous hyperplasia is characterized by intense proliferation of the glandular epithelium

Table VII. Cancer in the Phillippines*

	Breast	*Ovary*	*Corpus*	*Cervix*
No. of cases:				
College	485	74	59	120
High school	326	62	53	190
None	1,224	170	188	861
Relative risk†:				
College	1.84	2.02	1.46	0.65
High school	1.10	1.51	1.17	0.91
None	1.00	1.00	1.00	1.00

*After Hirayama and Basa.
†Control = other cancer group.

Table VIII. Incidence of uterine cancer in Israeli: Age-standardized rates per 100,000*

Origin	*Cervix*	*Corpus*	*Ratio, cervix/corpus*
Europe	4.21	11.86	0.35
Asia	4.30	4.96	0.86
Africa	10.89	5.44	2.00
N.W. Africa	11.89	3.55	3.34
Israeli Jews total	5.37	9.84	0.54

*From Steinitz, R., and Costin, C.: Israel J. Med. Sci. 7: 1420, 1971.

with proliferating glands frequently showing pseudostratification in a back-to-back pattern. There is an increasing order of severity in Types I, II, and III. In Type III, the severe form, the use of the term adenomatous hyperplasia (dysplasia) by Magnus Haines and Claud Taylor[48] seems appropriate. Though biologically a cancer precursor, we have refrained from calling Type III adenomatous hyperplasia cancer in situ, as some have, because of the impure criteria for invasion in the endometrium and because it is frequently reversible, especially in young women, by the exhibition of progestin or the induction of ovulation.

Raven and Roe[49] have referred to the difficulty in separating the stages in the development of cancer in hormone-target tissues and this is surely in accord with our experience in the case of endometrial carcinoma. We have diagnosed carcinoma in situ in our laboratory on infrequent occasions, when a cluster of endometrial glands exhibits anaplasia and free replication without apparent local restraint, yet apparently confined to a focus of well-differentiated malignant change, described in the past as adenoma malignum. This lesion is not reversible, though it may be removed at times by local excision—that is, curettage. This therapeutic observation should be considered in evaluating results of treatment of these lesions by hormonal manipulation.

Premenopausal adenomatous hyperplasia. This condition, occasionally discovered in young women with failure of ovulation, may be treated by induction of ovulation if infertility is a problem; in others, cycling with progestin will effect reversion to normal except for an occasional refractory endometrium.

Perimenopausal adenomatous hyperplasia. This is diagnosed by tissue sampling. While cytologic screening has a low rate of efficiency for endometrial cancer, if the sample is taken in conventional manner, it can diagnose endometrial cancer efficiently if the cytologic sample is taken directly from the endometrial cavity. However, to this date, very few cytologists claim accuracy in the diagnosis of endometrial cancer precursors. Our group has reported the accuracy of aspiration curettage[50] and we believe it should be used as a histologic screening measure, for it does not require anesthesia, for all high-risk women at the menopause and, perhaps, all menopausal women when we gain more experience.

If Type I or Type II adenomatous hyperplasia is found, one may choose to observe only with repeat tissue sampling at 6 month intervals or treat with progestin and then re-biopsy. Since we are dealing with a spectrum of disease, there will be some patients with Type II disease for whom hysterectomy will be preferred by patient and therapist.

With Type III adenomatous hyperplasia (dysplasia) and cancer in situ (adenoma malignum), a formal diagnostic curettage should follow aspiration curettage to rule out contiguous adenocarcinoma. For these lesions, cancer prophylaxis and definitive treatment of the accompanying uterine bleeding have been accomplished best in our hands by hysterectomy.

Postmenopausal adenomatous hyperplasia. With the recent fashion for so-called prophylactic estrogen for postmenopausal women, uterine bleeding frequently ensues. Aspiration curettage will reveal adenomatous hyperplasia in some, since this lesion will have been iatrogenically induced. It will suffice to observe only off hormonal medication and repeat the biopsy sample in 4 months unless bleeding continues. If bleeding occurs spontaneously without medication and adenomatous hyperplasia is detected by aspiration curettage, a formal diagnostic curettage under anesthesia is indicated, for a significant percentage will harbor true cancer. In those subjects in whom adenomatous hyperplasia is found, if they are generally fit, hysterectomy is indicated. Of course, if the administered estrogen has stimulated the production of a carcinoma, its treatment will follow already prescribed protocols (Fig. 2).

REFERENCES

1. Christopherson, W. M., Mendez, W. M., Parker, J. E., Lundin, F. E., Jr., and Ahuja, E. M.: Carcinoma of the endometrium: A study of changing rates over a 15-year period, Cancer **27:** 1005, 1971.
2. Taylor, C. W.: Premalignant change in the endometrium, Kellar, editor: *in* Modern Trends in Gynaecology, London, 1969, Butterworth & Company, Ltd.
3. Smith, D. C., Prentice, R., Thompson, D. J., and Hermann, W. L.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. **293:** 1164, 1975.
4. Cramer, D. W., Cutler, S. J., and Christine, B.: Trends in the incidence of endometrial cancer in the United States, Gynecol. Oncol. **2:** 130, 1974.
5. Doll, R., Muir, C., and Waterhouse, J., editors: Cancer Incidence in Five Continents; International Union Against Cancer, Berlin, 1970, Springer-Verlag, vol. 2.
6. Hirayama, T., National Cancer Center, Tokyo: Personal communication.
7. Ho, H. C., Hong Kong, U.I.C.C.: Monograph 1.10.
8. Shanmugaratnam, K.: Cancer in Singapore, Singapore Med. J. **14:** 69, 1973.
9. Haenszel, W., and Kurihara, M.: Studies of Japanese migrants, J. Natl. Cancer Inst. **40:** 43, 1968.
10. Stemmerman, G. N., and Lipkovic, P.: Carcinoma of the breast in Japanese women living in Hawaii, Gann **60:** 181, 1969.
11. Akazaki, K., and Stemmerman, G. N.: Comparative study of latent carcinoma of the prostate anong Japanese in Japan and Hawaii, J. Natl. Cancer Inst. **50:** 1137, 1973.
12. Cancer Mortality in U. S. A.: National Cancer Institute Monograph, 1971.
13. Masubuchi, K., Cancer Institute Hospital, Tokyo: Personal communication and Proceedings of International Cancer Congress, Florence, 1974.
14. Hirayama, T., and Basa: Philippine Tumor Registry and National Cancer Center, Tokyo; personal communication from T. Hirayama.
15. Steinitz, R., and Costin, C.: Cancer in Jewish immigrants, Israel J. Med. Sci. **7:** 1420, 1971.
16. Modan, B.: Role of ethnic background in cancer development, Israel J. Med. Sci. **10:** 1112, 1974.
17. Lipsett, M. B.: Hormones, nutrition and cancer, Cancer **35:** 3359, 1975.
18. Ablin, R. J., Bruns, P., Guinan, P., and Bush, I. M.: Effect of estrogen on the incorporation of H^3 by PHA-stimulated human peripheral blood lymphocytes, J. Immunol. **113:** 705, 1974.
19. Corscaden, J. A., and Gusberg, S. B.: The background of cancer of the corpus, Am. J. Obstet. Gynecol. **53:** 419, 1947.
20. Wynder, E. L., Escher, G. C., and Mantel, N.: An epidemiologic investigation of cancer of the endometrium, Cancer **19:** 489, 1966.
21. MacMahon, B.: Risk factors for endometrial cancer, Gynecol. Oncol. **2:** 122, 1974.
22. Dunn, J. E., Jr.: Geographic considerations of endometrial cancer, Gynecol. Oncol. **2:** 114, 1974.
23. Brown, J. B.: Urinary Oestrogen Excretion in the Study of Mammary Cancer, *in* Currie, editor: Endocrine Aspects of Breast Cancer, Edinburgh, 1958, E. & S. Livingstone, Ltd., p. 197.
24. MacMahon, B., Cole, P., Brown, J. B., Aoki, K., Lin, T. M., Morgan, R. W., and Woo, N. C.: Oestrogen profiles of Asian women and North American women, Lancet Oct. 23: 900, 1971.
25. Hausknecht, R. U., and Gusberg, S. B.: Estrogen metabolism in patients at high risk for endometrial carcinoma, Am. J. Obstet. Gynecol. **105:** 1161, 1969.
26. MacDonald, P. C., Gordin, J. M., and Siiteri, P. K.: Proc. Int. Congr. Endocrinol. **184:** 770, 1969.
27. Longcope, C.: Metabolic clearance and blood production rates of estrogens in postmenopausal women, Am. J. Obstet. Gynecol. **111:** 778, 1971.
28. Hausknecht, R. U., and Gusberg, S. B.: Estrogen metabolism in patients at high risk for endometrial cancer—II, Am. J. Obstet. Gynecol. **116:** 98, 1973.
29. MacDonald, P. C., and Siitemi, P. K.: Relationship between extraglandular production of estrone and the occurrence of endometrial neoplasia, Gynecol. Oncol. **2:** 259, 1974.
30. Rubin, B. L., Gusberg, S. B., Butterly, J., Han, T. C., and Maralit, M.: A screening test for estrogen dependence of endometrial carcinoma, Am. J. Obstet. Gynecol. **114:** 660, 1972.
31. Twombley, G. H., Scheiner, S., and Levitz, M.: Endometrial cancer, obesity and estrogen excretion in women, Am. J. Obstet. Gynecol. **82:** 424, 1961.
32. Schindler, A. E., Ebert, A., and Friedrich, E.: Conversion of androstenedione to estrone by human fat tissue, J. Clin. Endocrinol. Metab. **35:** 627, 1972.
33. Jensen, E. V.: Proceedings of International Congress of Biochemists, Vienna, 1958, London, 1960, Pergamon Press.
34. Brush, M. G., Taylor, R. W., King, R. J. B., and Kalinga, A. A.: J. Endocrinol. **41:** 12, 1968.
35. Brush, M. G., Taylor, R. W., and King, R. J. B.: Factors influencing steroid hormone levels; uptake of tritiated oestradiol by normal endometrium and by endometrial carcinoma; oestradiol binding, *in* Brush, Taylor, and Williams, editors: St. Thomas' Hospital Symposium on Endometrial Cancer, London, 1973, Wm. Heinemann.
36. Terenius, L., Lindell, A., and Persson, B. H.: Binding of estradio-17 to human cancer tissue of the female genital tract, Cancer Res. **31:** 1895, 1971.
37. McGuire, W. L., and Julian, J. A.: Comparison of macromolecular binding of estradiol in hormone dependent and hormone independent rat mammary carcinoma, Cancer Res. **31:** 1440, 1971.
38. Jensen, E. V., Block, G. E., Smith, S., Kyser, K., and DeSombre, E. R.: Estrogen receptors and breast cancer response to adrenalectomy, Natl. Cancer Inst. Monogr. **34:** 55, 1971.
39. Gusberg, S. B.: Precursors of corpus carcinoma estrogens and adenomatous hyperplasia, Am. J. Obstet. Gynecol. **54:** 905, 1947.
40. Gusberg, S. B., Moore, David, and Martin, Frederick: Precursors of corpus cancer—II, Am. J. Obstet. Gynecol. **68:** 1472, 1954.
41. Gusberg, S. B., and Hall, R. E.: Precursors of corpus cancer—III, Obstet. Gynecol. **17:** 397, 1961.
42. Gusberg, S. B., and Kaplan, A.: Precursors of corpus cancer. IV. Adenomatous hyperplasia as Stage 0 carcinoma of the endometrium, Am. J. Obstet. Gynecol. **87:** 662, 1963.
43. Gusberg, S. B., and Kardon, P.: Proliferative endometrial response to theca-granulosa cell tumors, Am. J. Obstet. Gynecol. **111:** 633, 1971.
44. Ziel, H. K., and Finkle, W. D.: Carcinoma among users of conjugated estrogen, N. Engl. J. Med. **293:** 1167, 1975.
45. Cullen, T. S.: Cancer of the Uterus, New York, 1900, Appleton.
46. Gusberg, S. B., Chen, S. Y., and Cohen, C. J.: Endometrial cancer: Factors influencing the choice of treatment, Gynecol. Oncol. **2:** 308, 1974.
47. Gusberg, S. B.: The dysfunctional and the neoplastic:

Clinical investigation in the service of patient care in endometrial cancer, AM. J. OBSTET. GYNECOL. **116:** 175, 1973.
48. Haines, M., and Taylor, C. W.: Gynecological Pathology, London, 1962, J. & A. Churchill, Ltd.
49. Raven, R. W., and Roe, F. J. C.: Prevention of Cancer, London, 1967, Butterworth & Company, Ltd.
50. Cohen, C. J., Gusberg, S. B., and Koffler, D.: Histologic screening for endometrial cancer, Gynecol. Oncol. **2:** 279, 1974.
51. Tseng, L., and Gurpide E.: Nuclear concentration of estriol in superfused human endometrium: Competition with estradiol, J. Steroid Biochem **5:** 273, 1974.

Cancer risk in diethylstilbestrol-exposed offspring

RICHARD F. MATTINGLY, M.D.
ADOLF STAFL, M.D., PH.D.
Milwaukee, Wisconsin

The occurrence of columnar epithelium in the vagina (vaginal adenosis) in young women with intrauterine exposure to diethylstilbestrol (DES) during the first trimester of pregnancy was observed in 231 patients (82 per cent of 280 cases who underwent colposcopic study.) Extension of columnar epithelium onto the portio of the cervix was present in the remaining 18 per cent of the cases. Abnormal colposcopic findings were present in the transformation zone in 96 per cent of the patients with vaginal adenosis. Directed biopsy revealed four cases of vaginal and/or cervical squamous carcinoma in situ (CIS), two cases of severe dysplasia, five cases of moderate, and 29 cases of mild dysplasia. The prevalence of CIS in DES-exposed girls (1.4 per cent) was nearly five times the prevalence rate of CIS in a control group of 5,808 DES-unexposed women (0.44 per cent). This finding correlates well with the hypothesis that the genesis of squamous intraepithelial neoplasia is specifically related to the extent and surface area of the vaginal transformation zone. An unusual case of invasive squamous carcinoma in a DES-exposed young girl is presented, which represents the initial observation of this association to date. (AM. J. OBSTET. GYNECOL. 126: 543, 1976.)

WITH THE RECOGNITION of the teratogenic effect of diethylstilbestrol on the maldevelopment of the lower genital tract, the major clinical concern has been related to the association of vaginal adenosis and clear-cell adenocarcinoma in DES-exposed young women.[1–3] In 1974, Stafl and Mattingly[4] expressed the initial concern that the major clinical risk in DES-exposed women was the development of squamous neoplasia of the vagina and cervix, rather than clear-cell adenocarcinoma. Our initial experience with 131 cases of DES-related vaginal adenosis demonstrated two cases of vaginal carcinoma in situ and five cases of dysplasia. The hypothesis of an increased risk of squamous neoplasia was based on previous colposcopic, histologic, and vascular studies on the transformation zone of the cervix.[5–8] However, at that time there were only short-term follow-up studies of the natural history of columnar epithelium in the vagina (vaginal adenosis) and the number of cases of vaginal intraepithelial neoplasia was limited. While the original hypothesis lacked sufficient data for immediate confirmation, additional information from this clinic and from other institutions provides the background for this report.

Presented as Guest Speaker at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Richard F. Mattingly, M.D., Depart. of Gynecology and Obstetrics, The Medical College of Wisconsin, 8700 West Wisconsin Ave., Milwaukee, Wisconsin 53226.

Materials and methods

Between June, 1971, and January, 1976, 280 young women whose mothers were given diethylstilbestrol (DES) during the first trimester of pregnancy were examined. Their ages ranged from 13 to 26. A total of 228 girls (81 per cent) were asymptomatic and were referred for colposcopic evaluation. Thirty-nine women (14 per cent) had a consistent mucous vaginal discharge and 13 girls (5 per cent) came for gynecologic consultation with the chief complaint of dyspareunia. Clinical evaluation included a gynecologic history, cytology from the cervix and from the vagina, and a careful pelvic examination. Except for one case of a benign ovarian cyst, the pelvic examination in all girls was negative.

After insertion of the self-retaining speculum, the cervix was grossly inspected and then colposcopic examination was performed. The colposcopic examination was done without anesthesia except in two girls who had a very tight hymen and where significant vaginal discharge was an indication for examination under anesthesia. The cervical mucus was cleaned from the cervix and vagina with gauze. Colposcopic

Table I. Gross examination

	No. of patients	*Per cent*
Vaginal hood	61	22
Cock's comb	35	13
Erythroplakia	15	5
Transverse septum	3	1
No changes	166	59

Table II. Extension of columnar epithelium

	No. of patients	*Per cent*
Lower third of vagina	17	6
Mid third of vagina	57	20
Upper third of vagina	74	26
Vaginal fornices	83	30
Cervix, portio	49	18

Table III. Colposcopic findings in 231 cases of vaginal adenosis

No. of patients	*Per cent*	*No. found*
Normal colposcopy	9 (4)	
Columnar epithelium		7
Transformation zone		2
Abnormal colposcopy	222 (96)	
White epithelium		67
Punctation		58
Mosaic		97

Table IV. Histologic findings

	No. of patients
Mild dysplasia	29
Moderate dysplasia	5
Severe dysplasia	2
Carcinoma in situ	4

examination was performed both before and after the acetic acid test. Full inspection of the vagina was achieved by rotation and slow withdrawal of the blades of the speculum. In patients where an abnormal colposcopic lesion was present, either on the cervix or in the vagina, a directed biopsy from the most suspicious colposcopic area was obtained without anesthesia with the Kevorkian forceps. A color colpophotograph of the cervical and vaginal lesions was obtained prior to biopsy.

Results

Visual examination of the cervix and vagina revealed four atypical gross findings—a vaginal hood, cock's-comb appearance of the cervix, erythroplakia, and transverse vaginal septum—all of which have been described previously.[9] The frequency of these findings is recorded in Table I.

Colposcopic findings. The main objective of the colposcopic examination was to identify the location of the original squamocolumnar junction. This was established by identification of the extent of the colposcopic transformation zone, the presence of gland openings and Nabothian cysts, and by the differences in the vascular pattern of the transformation zone and the original squamous epithelium. The location of the original squamocolumnar junction is shown in Table II. In identifying the border between the cervix and vagina, we considered the area where the mucosa could be folded and was loosely attached to the stroma of the cervix. The vaginal hood was considered to be a portion of the vagina, which is an admitted difference in the interpretation of this study from the opinion of Herbst and co-workers.[2]

In 231 patients (82 per cent), the original squamocolumnar junction was found in the vagina. In nine of the 231 cases (4 per cent), the colposcopic findings were normal with either normal columnar epithelium or a normal transformation zone. In 222 cases (96 per cent), the colposcopic findings in the vaginal transformation zone were abnormal and included a mosaic pattern in 42 per cent, punctation in 22 per cent, and white epithelium in 29 per cent of patients (Table III).

Histologic findings. One of the initial objectives in the early part of this study was to demonstrate, histologically, the presence of the columnar epithelium in the vaginal mucosa, i.e., vaginal adenosis.[9] Because of the colposcopic accuracy in identifying the presence of the columnar epithelium (vaginal adenosis), the major emphasis of this study was directed toward the histologic changes associated with the abnormal colposcopic lesions in the vagina and cervix. Biopsies were taken from the most suspicious colposcopic lesion. While the abnormal colposcopic lesion in the vagina appears more significant to the less-experienced observer than the actual histologic changes, the liberal application of acetic acid produces blanching of the epithelium and a marked color change. However, after careful evaluation of the important colposcopic factors for grading of the degree of neoplasia, mainly the vascular pattern and intercapillary distance, the diagnostic criteria are the same in the vagina as on the cervix.

The directed biopsy revealed four cases of vaginal and/or cervical squamous carcinoma in situ (Figs. 1 and 2), two cases of severe dysplasia, five cases of moderate dysplasia, and 29 cases of mild dysplasia (Table IV). The clinical summary of the four cases of vaginal car-

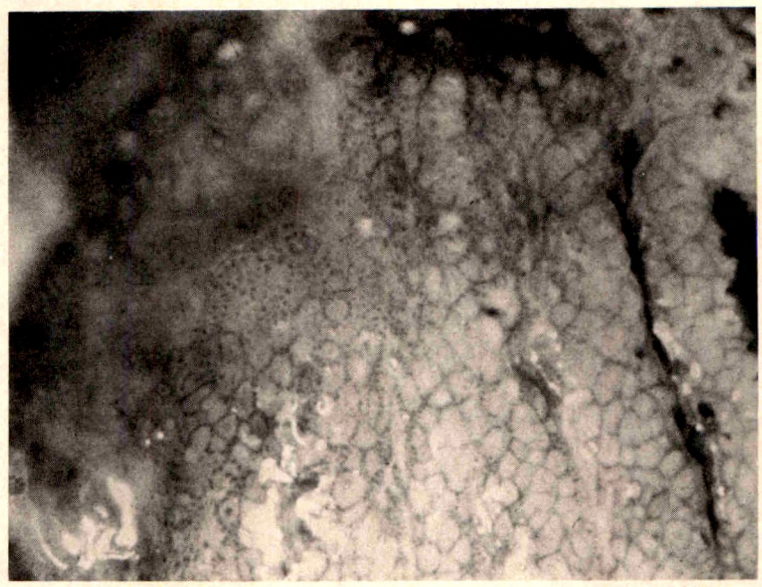


Fig. 1. Large area of mosaic pattern with significantly increasing intercapillary distance extending from the cervix into the anterior vaginal fornix. Colposcopic impression, carcinoma in situ.

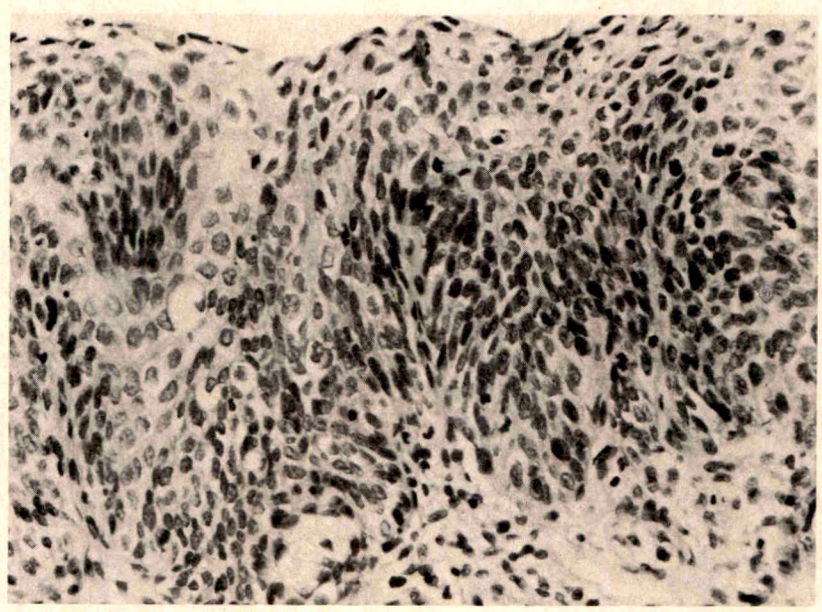


Fig. 2. Representative histologic changes from the biopsy described in Fig. 1 with full-thickness loss of stratification, loss of cellular polarization, and marked nuclear pleomorphism, compatible with carcinoma in situ. (×400.)

cinoma in situ and two cases of severe dysplasia are included in Table V.

An unusual case of invasive squamous carcinoma of the cervix and vagina in a young girl with DES exposure is presented in detail.

Case report

M. W., a 19-year-old, para 1-0-2-1, white woman with documented intrauterine DES exposure, was initially seen in another institution in April, 1975, because of vaginal bleeding. A Pap smear was reportedly negative 8 months earlier when seen for profuse mucoid vaginal discharge. Colposcopic examination was not available to the initial examiner and was not performed. The disease was initially diagnosed as an invasive squamous carcinoma of the cervix with extension into the posterior vagina, Stage II-A. The biopsy (Figs. 3 and 4) confirmed this diagnosis of an infiltrating squamous-cell carcinoma. The patient was treated

Table V. Clinical summary of histologic findings

Initials	*Age*	*Sexually active*	*Pap smear*	*Colposcopy*	*Localization of squamocolumnar junction*	*Parity*	*Symptoms*	*Gross appearance*	*Histology*
C. L.	22	yes	Atypical	White epithelium	Upper third of vagina	0	0	Cock's comb	Squamous carcinoma in situ
N. H.	22	yes	Suspicious	Mosaic punctation	Fornix	0	0	0	Squamous carcinoma in situ
T. R.	21	yes	Atypical	Mosaic	Fornix	2	0	Hood	Squamous carcinoma in situ
K. C.	25	yes	Suspicious	Mosaic	Fornix	0	0	0	Squamous carcinoma in situ
J. D.	20	yes	Negative	Mosaic	Lower third of vagina	0	0	0	Severe dysplasia
K. K.	21	yes	Suspicious	Mosaic	Fornix	2	0	0	Severe dysplasia

Table VI. Cancer risk in DES-exposed women

	MCGH	*MCGH controls*
	DES exposed	*DES unexposed*
No. of patients	280	5,808
No. of carcinoma in situ	4	19
Prevalence rate (%)	1.4	0.3
Increased DES cancer risk	4.66*	

*($p < 0.05$).

with intracavitary radium and external beam irradiation therapy at another institution, receiving a combined midpelvic irradiation dosage of approximately 5,000 rads. A follow-up examination 5 months later, in September, 1975, revealed recurrent squamous-cell carcinoma on biopsy of the outer one third of the vagina. The patient was not a candidate for an exenteration, in view of the fixation of the tumor to the lateral pelvic wall and bilateral ureteral obstruction. The patient died with uremia in January, 1976, 9 months after the initial treatment.

Comment

The current study of 280 young women with a positive history of intrauterine exposure to DES revealed observations similar to those previously reported from this clinic, including clinical symptoms, gross and histologic findings, and the extension of the transformation zone. The challenging finding of this study was the occurrence of an invasive squamous-cell carcinoma of the cervix and vagina in a DES-exposed young girl. This report represents the initial observation of this association. Unfortunately, this patient did not have the benefit of a colposcopic examination prior to the diagnosis and treatment of this malignancy and, therefore, the development of an invasive squamous carcinoma in vaginal adenosis is not conclusive. However, this presumed association is based on the long-standing history of a mucoid vaginal discharge, the young age of the patient, the documented intrauterine exposure to DES during the first trimester, the extension of the lesion into the upper vagina, and the rarity of such an advanced stage of a primary cervical carcinoma in this age group. While the conclusive histologic evidence is lacking in this case concerning the development of invasive squamous carcinoma from pre-existing columnar epithelium in the vagina, this relationship was clearly documented in two recent cases of primary vaginal carcinoma as reported by Veridiano, Weiner, and Tancer.[10] In both of these latter cases, the cervix was histologically negative and the squamous-cell carcinoma originated in the vagina. Furthermore, in both of these cases, there was colposcopic and histologic documentation of benign adenosis on the margin of the squamous-cell carcinoma of the vagina.

The association of prior DES exposure in these cases of primary squamous-cell carcinoma of the vagina is of clinical interest in the pathogenesis of squamous-cell carcinoma of the lower genital tract. While there is historical evidence of the absence of DES exposure in both of these latter cases, the presence of an extensive vaginal transformation zone was documented. It is clinically recognized that vaginal adenosis may be present in the absence of DES exposure, although this finding is uncommon (less than 3 per cent).[11, 12] However, the presence of vaginal adenosis is much more frequent in DES-exposed girls, in whom the frequency

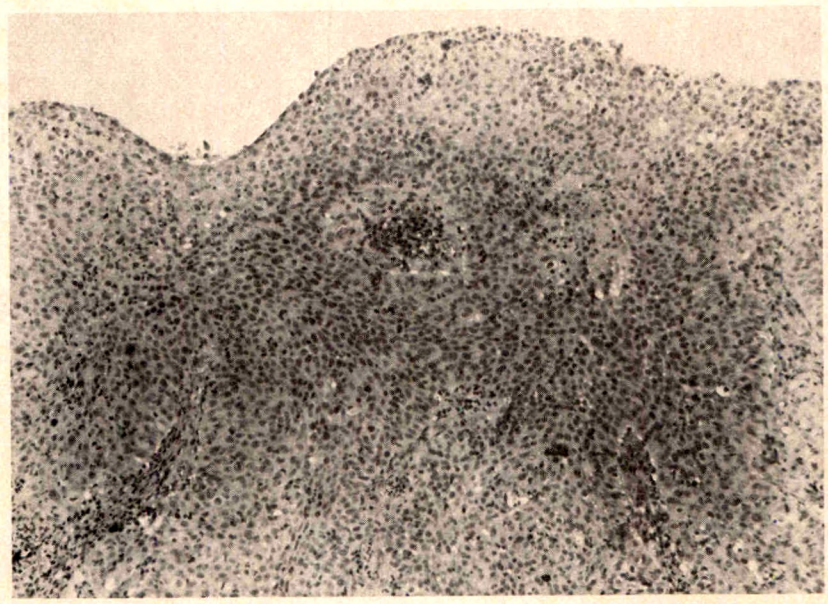


Fig. 3. Low-power histologic view of infiltrating squamous-cell carcinoma.

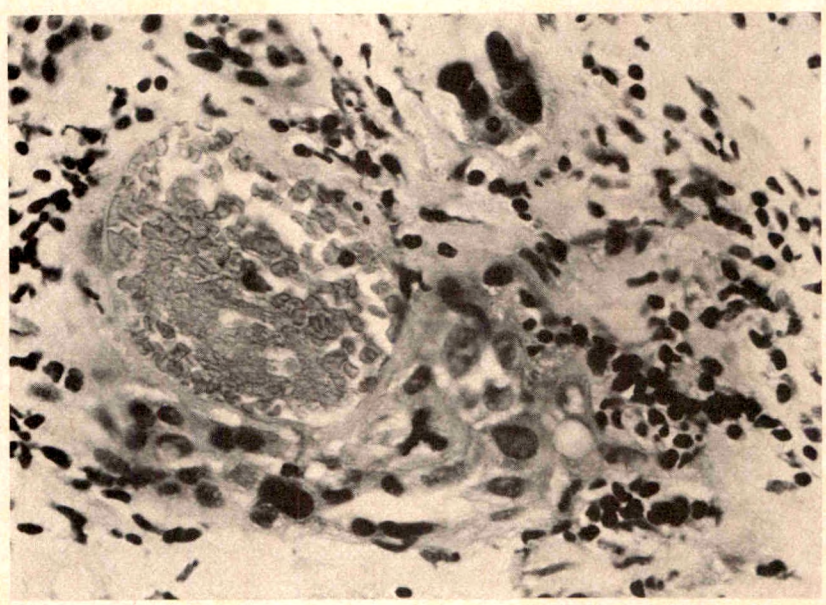


Fig. 4. Infiltrating squamous-cell carcinoma involving a perivascular space. A tripolar mitotic figure is evident at the margin of the blood vessel. (×400.)

of this condition has been reported from 30 to 91 per cent of such cases.[2, 3, 9, 13, 14]

Considering the potential cancer risk of these women with an extensive transformation zone, it is unimportant if the vaginal adenosis is DES related or not; more important is the extensiveness of the transformation zone. As previously proposed,[4] the probability of neoplastic transformation by carcinogens present in the vagina is significantly higher when the transformation zone is extensive. This additional clinical experience provides further support to the hypothesis that the biologic effect of DES is not carcinogenic, but teratogenic, and that DES induces an embryologic extension of columnar epithelium onto the ectocervix and vagina where the possibility of neoplastic change may occur at a later age by other mutangenic agent(s).[4]

From the previously reported cases of vaginal dysplasia and carcinoma in situ, the critical question arose if these changes represented true vaginal neoplasia or only immature metaplasia. Unfortunately, the

histology may not differentiate clearly between these two conditions. However, the cases of invasive squamous carcinoma of the vagina discussed in this report provide convincing evidence that squamous neoplasia can occur in these lesions.

The data from this study show that among the 280 patients in this series, four cases of vaginal and cervical carcinoma in situ were found, a prevalence rate of 1.4 per cent. Experience from the Mayo Clinic[15] also revealed four cases of cervical carcinoma in situ among 289 DES-exposed young women, a prevalence rate of 1.4 per cent. The similarity of the data from the Mayo Clinic and our clinic is striking. Among both study groups, eight cases of carcinoma in situ of the vagina and/or cervix were found in 568 patients for a prevalence rate of 1.4 per cent. As a control series, we reviewed the prevalence rate of cervical neoplasia in a group of DES-unexposed women who were examined in the gynecologic screening clinic of Milwaukee County General Hospital (MCGH) during the 7 year period ending in 1971. During the first examination of 20,905 asymptomatic women in this program, 93 cases of cervical carcinoma in situ were detected, for a prevalence rate of 0.44 per cent. Among these women, there were 5,808 women under the age of 30 years, in whom 19 cases of cervical carcinoma in situ were found for a prevalence rate of 0.3 per cent (Table VI). In comparing these data, the present study group of young DES-exposed patients had a nearly five times (4.66) higher prevalence rate of carcinoma in situ than the DES-unexposed women, which is statistically significant ($p < 0.05$). The average age in the entire DES study group was age 18, whereas the average age of the 5,808 DES-unexposed patients from the gynecologic screening clinic was 27 years. The patients in the DES study group are therefore much younger than the control patients and it is reasonable to expect that a much higher frequency of carcinoma in situ may occur during the next decade when the women in the DES group reach the comparable age group of the controls.

The experience of this ongoing colposcopic study of DES-exposed women provides additional evidence of the increased cancer risk in this group of patients. While the initial clinical concern centered on the infrequent occurrence of vaginal clear-cell adenocarcinoma in these young women, the current concern of the teratogenic effect of DES exposure relates to the squamous neoplastic change of an extended vaginal transformation zone by carcinogenic agents in the vagina. A nearly fivefold increase in the prevalence rate of carcinoma in situ of the lower genital tract in this DES study, as compared with a similar age group of DES-unexposed women, correlates well with the original hypothesis expressed from this clinic of the genesis of squamous intraepithelial neoplasia.[4]

This concept is specifically related to the extent and surface area of the transformation zone within the vagina. The potential increased occurrence of intraepithelial neoplasia of the lower genital tract during the next decade requires a critical refocusing of the initial concern for the infrequent occurrence of adenocarcinoma of the vagina to the more frequent development of squamous neoplasia in this high-risk group of young women.

REFERENCES

1. Herbst, A. L., Ulfelder, H., and Poskanzer, D. C.: Adenocarcinoma of the vagina, N. Engl. J. Med. **284:** 878, 1971.
2. Herbst, A. L., Kurman, R. J., Scully, R. E., and Poskanzer, D. C.: Clear-cell adenocarcinoma of the genital tract in young females, N. Engl. J. Med. **287:** 1259, 1972.
3. Ulfelder, H.: Stilbestrol, adenosis and adenocarcinoma, Am. J. Obstet. Gynecol. **117:** 794, 1973.
4. Stafl, A., and Mattingly, R. F.: Vaginal adenosis: A precancerous lesion? Am. J. Obstet. Gynecol. **120:** 666, 1974.
5. Stafl, A., Linhartova, A., and Dohnal, V.: Das Kolposkopische Bild der Feldorung und seine Pathogenese, Arch. Gynäkol. **199:** 223, 1963.
6. Stafl, A., and Linhartova, A.: Die Umwandlunszone und ihre Genese, Arch. Gynäkol. **204:** 228, 1967.
7. Stafl, A., Dohnal, V., and Linhartova, A.: Uber Kolposkopische, Histologische und Gefassbefunde an der Krankhaft veränderten Portio, Geburtshilfe. Frauenheilkd. **23:** 437, 1963.
8. Stafl, A., Linhartova, A., and Dohnal, V.: Das Kolposkopische Bild des Grundes, des papilaren Grundes, der atypischen Umwandlungszone und deren Pathogenese, Arch. Gynäkol. **204:** 212, 1967.
9. Stafl, A., Mattingly, R. F., Foley, D. V., and Fetherston, W. C.: Clinical diagnosis of vaginal adenosis, Obstet. Gynecol. **43(1):** 118, 1974.
10. Veridiano, N. P., Weiner, E. A., and Tancer, M. L.: Squamous cell carcinoma of the vagina associated with vaginal adenosis, Obstet. Gynecol. **47:** 689, 1976.
11. Linhartova, A.: Congenital ectopy of the uterine cervix, Int. J. Gynaecol. Obstet. **8:** 653, 1970.
12. Pixley, E.: Personal communication, 1973.
13. Herbst, A. L., Kurman, R. J., and Scully, R. E.: Vaginal and cervical abnormalities after exposure to stilbestrol in utero, Obstet. Gynecol. **40:** 287, 1972.
14. Sherman, A. I., Goldrath, M., Berlin, A., Vakhariva, V., Banooni, F., Michaels, W., Goodman, P., and Brown, S.: Cervical-vaginal adenosis in utero exposure to synthetic estrogens, Obstet. Gynecol. **44:** 531, 1974.
15. Noller, K. L., Decker, D. G., Fish, C. R., and Gaffey, T. A.: Presented at Annual Meeting of Soc. Gynecol. Oncol., Key Biscayne, Florida, January, 1976.

A comparison of oral prostaglandin E_2 and intravenous oxytocin for induction of labor in normal and high-risk pregnancies

GEORGE H. NELSON, PH.D., M.D.
C. I. BRYANS, JR., M.D.
Augusta, Georgia

The efficacy of oral prostaglandin E_2 (PGE_2) for induction of labor has been compared to that of intravenous oxytocin. There were 49 patients in each series. The over-all success rate with PGE_2 is 82 per cent; with oxytocin, 65 per cent. PGE_2 is at least as effective as oxytocin regardless of Bishop score or gravidity. There was no difference in the duration of labor in successful inductions with PGE_2 or oxytocin. Nausea and diarrhea are more common with PGE_2 but in only one case was this severe enough to warrent discontinuing the medication. One case of uterine hypertonus occurred in each series. No serious harmful effects on mother or fetus were noted with PGE_2. These data support the concept that oral PGE_2 administration is a safe and effective alternative to intravenous oxytocin for induction of labor in normal and high-risk pregnancies.
(AM. J. OBSTET. GYNECOL. 126: 549, 1976.)

ORAL PROSTAGLANDIN E_2 (PGE_2) was first demonstrated by Karim and Sharma[7] in 1971 to be an effective agent for induction of labor. Since then, other investigators[1-6, 8-10, 12, 13] have reported their experiences. In addition, Noah[11] of the Upjohn Company recently summarized their data in 585 patients.

It is the purpose of this communication to report our results in 49 oral PGE_2 inductions and to compare these with data from an equal number of intravenous oxytocin inductions.

Materials and methods

All patients included in the study were admitted to the obstetrics service of the Eugene Talmadge Memorial Hospital in Augusta, Georgia. The PGE_2 inductions were done between April and September, 1974, and the oxytocin inductions between October, 1974, and July, 1975. PGE_2 was given in the form of 0.5 mg. tablets manufactured by the Upjohn Company. The oxytocin was administered as a solution containing 40 mU. per milliliter. The dosage of oxytocin was controlled by a Harvard infusion pump. In most cases, labor was monitored by an external monitor. In some cases intrauterine pressure measurements were made with an internal catheter; however, these were too few to yield any meaningful results.

Fifty-one patients were started on the PGE_2 protocol and 50 on oxytocin. However, in two PGE_2 patients and one oxytocin patient the decision was made early in the induction to stop the induction and proceed with cesarean section for reasons not related to the oxytocic agent. Therefore, these were dropped from the study and the present report is concerned with the remaining 49 patients in each group.

The indications for induction are listed in Table I. The gestational ages at the time of the inductions are shown in Table II. The obstetric estimates were made prior to the inductions and the pediatric estimates were made from physical examination of the neonate.

The PGE_2 and oxytocin dosage schedules are outlined below:

PGE_2 dosage schedule:

1. Begin with 0.5 mg. and repeat in 1 hour.
2. At 2 hours, dose increased to 1.0 mg. if necessary.
3. At 3 hours, dose increased to 1.5 mg. if necessary.

From the Department of Obstetrics and Gynecology, Medical College of Georgia.

Presented by invitation at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. George Nelson, The Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta, Georgia 30902.

Table I. Indications for induction

	PGE_2	Oxytocin
Hypertensive disease	16	17
Elective induction	12	7
Post term (42 weeks or more)	10	7
PROM	3	8
Hyptertensive disease and post term	0	4
Rh sensitization	2	2
Fetal death	1	2
Diabetes	1	1
Diabetes and fetal death	1	0
Diabetes and hypertension	1	1
PROM and hypertension	1	0
PROM and post term	1	0
	49	49

Table II. Gestational age at time of induction

	By obstetric estimate		*By pediatric estimate**	
Gestational age (wk.)	PGE_2	Oxytocin	PGE_2	Oxytocin
42 or >	11	11	1	0
40-41	16	12	27	33
38-39	14	20	12	9
36-37	5	4	3	5
34-35	2	1	2	0
32-33	0	1	1	0
30-31	1	0	1	0
Total	49	49	47	47

*No pediatric estimate of gestational age in two stillbirths in each group.

4. Quality of labor evaluated every hour. When good labor established, dose usually decreased to 0.5 mg.
5. At each subsequent hour, dose determined by the quality of labor.
6. Maximum dose allowed 1.5 mg. per hour.

Oxytocin dosage schedule:

1. Begin at 2 mU. per minute.
2. At the end of each hour, dose doubled, if necessary, until a maximum of 16 mU. per minute reached.

The PGE_2 dosage schedule is the same as that described by Noah[11] as "Low incremental."

A successful PGE_2 or oxytocin induction is defined as the achievement of complete cervical dilatation with either PGE_2 or oxytocin alone.

In three successful oxytocin inductions, the dose of oxytocin was increased above 16 mU. per minute after 8 hours of induction. In two cases, the dose was increased to 20 mU. per minute and in one case to 30 mU. per minute.

A failed PGE_2 induction is defined as follows: (1) the induction was stopped after at least 8 hours of PGE_2; (2) PGE_2 was discontinued after at least 8 hours and the induction continued with oxytocin; or (3) the induction was stopped because of side effects thought to be directly related to PGE_2. A failed oxytocin induction is one in which the induction was stopped after at least 8 hours of oxytocin.

Table III. Over-all outcome of PGE_2 and oxytocin induction

	PGE_2	Oxytocin
No.	49	49
Success:		
Delivered vaginally	38	31
Completely dilated—CPD	2	1
Cesarean section		
Total	40	32
Failure:		
Subsequent delivery with oxytocin	5	9
Subsequent spontaneous delivery	0	6
Cesarean section	4	2
Total	9	17

Results

The over-all success and failure rates are shown in Table III. As can be seen, the success rate with PGE_2 was slightly higher than with oxytocin.

The relationship between Bishop score and outcome is demonstrated in Table IV. The mean Bishop score in the PGE_2 inductions was 6.4, whereas it was 5.3 in the oxytocin inductions. Perhaps the fact that the PGE_2 patients were slightly more favorable explains the fact that the success rate in the PGE_2 group was slightly higher. While no statistics have been applied to these data because of the small numbers, there is the suggestion that perhaps PGE_2 is more effective when the Bishop score is low. If we look at Bishop scores of 5 or less, the success rate with PGE_2 was 12 out of 17 (71 per cent); with oxytocin it was 14 out of 28 (50 per cent).

The relationship between gravidity and outcome is shown in Table V. In the PGE_2 group, the suggestion that there might be a slightly higher success rate in the primigravid group over the multigravid group might be explained by the fact that the average Bishop score was higher in the primigravid patients. However, in combining data in both groups, the success rates are as follows: gravida 1, 77 per cent; 2, 73 per cent; 3 to 4, 74 per cent; five or more, 68 per cent. Surely, no trend is apparent.

The relationship between rupture of membranes and outcome is shown in Table VI. As can be seen, the

Table IV. Relationship between Bishop score and outcome of induction

	Induction							
	PGE_2				*Oxytocin*			
Bishop score	*Attempts*	*Successes*	*Failures*	*Per cent success*	*Attempts*	*Successes*	*Failures*	*Per cent success*
0-2	3	1	2	33	4	1	3	25
3-5	14	11	3	79	24	13	11	54
6-8	25	21	4	84	16	13	3	81
9-11	7	7	0	100	5	5	0	100
Total	49	40	9	82	49	32	17	65

Table V. Relationship between gravidity and outcome of induction

	Induction							
	PGE_2				*Oxytocin*			
Gravidity	*Attempts*	*Successes*	*Failures*	*Per cent success*	*Attempts*	*Successes*	*Failures*	*Per cent success*
1	12	11	1	92	14	9	5	64
2	14	11	3	79	12	8	4	67
3-4	15	13	2	87	12	7	5	58
5 or >	8	5	3	60	11	8	3	73
Total	49	40	9	82	49	32	17	65

Table VI. Relationship between rupture of membranes and outcome of induction

	Induction							
	PGE_2				*Oxytocin*			
Membranes ruptured	*Attempts*	*Successes*	*Failures*	*Per cent success*	*Attempts*	*Successes*	*Failures*	*Per cent success*
Before induction	10	9	1	90	9	9	0	100
During induction	33	31	2	94	24	23	1	96
Unruptured at termination of induction	6	0	6	0	16	0	16	0
Total	49	40	9	82	49	32	17	65

occurrence of intact or ruptured membranes at the start of the induction is about equal. As would be expected, rupture of the membranes at the start of the induction was associated with a high success rate. It is also apparent that, in most of the failed inductions, the membranes were still intact at the end of the induction attempt.

The duration of labor in successful inductions with vaginal delivery is shown in Tables VII and VIII. It is apparent that there is very little difference in the duration of labor between the two series. As might be expected, the labor was shorter in both groups when the Bishop score was high (i.e., 9 to 11).

A comparison of Apgar scores in successful vaginal deliveries is shown in Table IX. The similarity between the two groups is remarkable.

Table X lists the side effects. It would appear that nausea and diarrhea are more frequent with PGE_2 than with oxytocin.

Comment

The over-all success rate of 82 per cent with oral PGE_2 compares favorably with previous reports.[1–13] However, accurate comparisons with these are difficult because of variation in dosage schedules, in requirements for rupture of the membranes, and in the definition of success and failure. Surely, in this study, the success rate with oral PGE_2 is at least as favorable as with intravenous oxytocin.

As shown in Table VI and as would be expected, rupture of the membranes plays an important role in the success or failure of any oxytocic agent. In this

Table VII. Relationship between Bishop score and duration in successful inductions with vaginal delivery

	PGE_2			Oxytocin		
		Duration of induction (min.)			Duration of induction (min.)	
Bishop score	No.	Mean	Range	No.	Mean	Range
0-2	1	395		1	612	
3-5	10	493	(206-865)	12	455	(202-767)
6-8	20	439	(114-645)	13	470	(193-1,000)
9-11	7	280	(173-510)	5	298	(153-541)
Total	38	423	(114-865)	31	447	(153-1,000)

Table VIII. Relationship between gravidity and duration in successful inductions with vaginal delivery

	PGE_2			Oxytocin		
		Duration of induction (min.)			Duration of induction (min.)	
Gravidity	No.	Mean	Range	No.	Mean	Range
1	10	442	(173-652)	8	493	(290-1,000)
2	11	424	(114-865)	8	500	(218-657)
3-4	12	469	(206-655)	7	333	(153-527)
5 − >	5	305	(180-405)	8	426	(193-720)

Table IX. Apgar scores in successful inductions with vaginal delivery

	Apgar score				
	1, 2	3, 4	5, 6	7, 8	9, 10
PGE_2:					
1 minute	0 (0%)	2 (6%)	2 (6%)	10 (28%)	22 (61%))
5 minute	0 (0%)	0 (0%)	1 (3%)	1 (3%)	34 (94%)
Oxytocin:					
1 minute	1 (3%)	0 (0%)	0 (0%)	8 (28%)	20 (69%)
5 minute	0 (0%)	1 (3%)	0 (0%)	1 (3%)	27 (93%)

Table X. Side effects

	PGE_2		Oxytocin	
	No.	%	No.	%
None	33	67	42	86
Nausea	7	14	0	0
Vomiting	5	10	3	6
Diarrhea	8	16	0	0
Uterine hypertonus	1 (10 min.)	2	1 (10 min.)	2
Tachycardia	1	2	0	0
Tumultuous terminal labor	3	6	2	4
Headache	0	0	1	2

study, the resident in charge of the induction was at liberty to rupture the membranes when he considered it appropriate to do so. They were not ruptured at any specified time. As a rule, the membranes were ruptured when the patient was considered to be in good labor and the head became engaged. Any mandatory requirement for rupture of the membranes would probably have had a significant effect on the results. It is also apparent from Table VI that failure to rupture the membranes during the course of the induction attempt was associated with most of the failed inductions. However, the majority of these cases were in patients who did not establish a satisfactory labor pattern during the course of the 8 hour induction attempt and the fetal heads remained unengaged. Therefore, rupture of the membranes was not considered indicated in those particular patients.

From Tables VII and VIII, one can also see that the duration of labor with PGE_2 is comparable with that of oxytocin.

No serious harmful effects attributable to PGE_2 were noted either during labor and delivery or in the subsequent hospital stay. In one patient the PGE_2 was stopped after 6 hours because of a combination of poor labor and diarrhea. We had one case of uterine hypertonus in each group with each case lasting about 10 minutes. These were clinical diagnoses as the external monitor was being used in each case. In the case of hypertonus in the PGE_2 group, the infant had Apgar scores of 9 and 10; in the case in the oxytocin group, the infant had Apgar scores of 1 and 3. In the latter case, the hypertonus occurred about 5 hours prior to delivery. This was a breech presentation and there was evidence of fetal distress for the last 25 minutes prior to delivery. Therefore, in our opinion the uterine hypertonus was not responsible for the depression of this infant at birth. In addition, it is very difficult from this study to know if vomiting per se is specifically associated with PGE_2 inductions. Of the five PGE_2 patients who vomited, three of these were in advanced labor and two of these three also had received intravenous Demerol shortly before the vomiting occurred. Only one of the three oxytocin patients who vomited was in advanced labor and none of the episodes of vomiting seemed to be related to any medication. Therefore, in two patients in each group the vomiting seemed to be related to nothing other than the fact that the patients were in labor. Also, since increased drowsiness has been observed with PGE_2 inductions, we would like to state that this was not noted in our series.

In addition to the data reported here, we have measurements of temperature, pulse, respiration, blood pressure, and blood and urine chemistries. This will be reported at a later date.

The results of this study support the concept that oral PGE administration is a safe and effective alternative to intravenous oxytocin infusion for induction of labor in normal and high risk pregnancies.

The authors are greatly indebted to Dr. Melvin L. Noah and the Upjohn Company for their generous support of this study.

REFERENCES

1. Barr, W., and Naismith, W. C. M. K.: Oral prostaglandins in the induction of labour, Br. Med. J. **2:** 188, 1972.
2. Basu, H. K., and Rajan, K. T. J.: Induction of labor with prostaglandin E_2 tablets, J. Int. Med. Res. **3:** 73, 1975.
3. Corson, S. L., and Bolognese, R. J.: Oral prostaglandin E_2 for induction of labor, J. Reprod. Med. **12:** 167, 1974.
4. Craft, I.: Amniotomy and oral prostaglandin E_2 titration for induction of labour, Br. Med. J. **2:** 191, 1972.
5. Friedman, E. A., and Sachtleben, M. R.: Oral prostaglandin E_2 for induction of labor at term, Obstet. Gynecol. **43:** 178, 1974.
6. Friedman, E. A., Sachtleben, M. R., and Green, W.: Oral prostaglandin E_2 for induction of labor at term. II. Comparison of two low-dosage regimens, Am. J. Obstet. Gynecol. **123:** 671, 1975.
7. Karim, S. M. M., and Sharma, S. D.: Oral administration of prostaglandins for the induction of labour, Br. Med. J. **1:** 260, 1971.
8. Kelly, J., Flynn, A. M., and Bertrand, P. V.: A comparison of oral prostaglandin E_2 and intravenous syntocinon in the induction of labour, J. Obstet. Gynaecol. Br. Commonw. **80:** 923, 1973.
9. Miller, J. F., Welply, G. A., and Elstein, M.: Prostaglandin E_2 tablets compared with intravenous oxytocin in induction of labor, Br. Med. J. **1:** 14, 1975.
10. Murnaghan, G. A., Lamki, H., Rashid, S., et al.: Induction of labour with oral prostaglandin E_2, J. Obstet. Gynaecol. Br. Commonw. **81:** 141, 1974.
11. Noah, M.: Prostaglandins promise more effective fertility control, Population Reports, Series G, No. 6, G59-60, 1975.
12. Thiery, M., Le Sian, A. Y., de Hemptinne, D., et al.: Induction of labour with prostaglandin E_2 tablets, J. Obstet. Gynaecol. Br. Commonw. **81:** 303, 1974.
13. Yip, S. K., Ma, H. K., and Ng, K. H.: Induction of labour with oral prostaglandin E_2, J. Obstet. Gynaecol. Br. Commonw. **80:** 442, 1973.

Discussion

Dr. Charles H. Hendricks, Chapel Hill, North Carolina. Dr. Nelson has concluded that orally administered PGE_2 is an effective and safe alternative to intravenous oxytocin for the induction of labor. I would like to comment in some detail about this conclusion. First, there is the matter of effectiveness. Dr. Nelson has demonstrated from his own study effectiveness of this dosage of prostaglandin in the induction of labor. His good results confirm those reported in a number of other series totalling hundreds of cases.

The process by which the cervix becomes "ripened" continues to be pretty much of a mystery, especially when oxytocin is utilized to perform this function. In recent years hope has been expressed that prostaglandin, or a prostaglandin analogue, might prove to be capable of bringing about cervical ripening more or less independently from the induction of large amounts of uterine contractility. This hope has been strengthened by the observation of Liggins and Short,[1] who showed in the sheep that a continuous intravenous infusion of prostaglandin $F_{2\alpha}$ over a 24 hour period completely prepared the sheep cervix for partuition. The low dose employed in the sheep was not sufficient to induce any evidence of uterine contractility. In the human subject, however, careful studies employing small doses of orally administered PGE_2 have failed to demonstrate convincingly that this preparation is effective in cervical preparation to the degree that it would be capable of altering the duration and characteristics of subsequent labor.

One might query Dr. Nelson about some aspects of patient management. One of these queries concerns the practice of rupture of the membranes. Dr. Nelson stated that the physician in charge of the induction "was at liberty to rupture the membranes when he considered it appropriate to do so" and that usually the membranes were ruptured when the head became engaged. It seems curious to me that six of the nine prostaglandin failures and 16 of the 17 oxytocin failures had membranes intact at the completion of the induction trial. I wonder if Dr. Nelson might not have anticipated a higher percentage of successes if the membranes had been ruptured during induction in some of these cases. Another possibility, of course, might be that in a significant proportion of these individuals the head did not become engaged and thus the physician did not consider it appropriate to perform the amniotomy. If such were the case, one would anticipate a higher percentage of failures under these conditions. One notes that there were 17 of the prostaglandin patients with Bishop scores of 5 or less, whereas 28 of the oxytocin patients had Bishop scores of 5 or less. It appears that most of these low Bishop scores were among the oxytocin failures and that amniotomy had not been done in the great majority of these failure cases for some reason which is not made clear in the paper. At any rate, it should be emphasized that the percentage of success of the induction of labor

is destined always to be directly related to the degree of labor readiness of the cervix at the time the induction is initiated.

In one instance in the oxytocin series the infant had Apgar scores of 1 and 3 at 1 and 5 minutes, respectively. This was a breech presentation. One episode of hypertonus was documented about 5 hours before delivery and there was evidence of fetal distress for the last 25 minutes prior to delivery. I would like to ask Dr. Nelson if there were any other infants presenting as breeches in either series and if, from his own experience, he would prefer to manage breech presentation by oxytocin induction, by prostaglandin induction, or by some other method.

I must take exception to Dr. Nelson's unqualified statement that oral PGE_2 is a safe alternative to oxytocin for the induction of labor. In the first place, no oxytocic agent yet discovered is capable of conferring immunity from disaster when it is incorrectly used. Oral PGE_2, like other agents, has already been associated with rupture of the uterus in a woman who had had a previous uterine scar.[2] Friedman and Sachtleben[3] observed hypertonus in three of the 45 cases of labor induction reported by them. The episodes of hypertonus do not appear to be specifically dose-related in that two of Friedman's 15 cases occurred when the dose was lower than that employed by Dr. Nelson and the third case of hypertonus occurred in a case where the dosage was higher than that used by Dr. Nelson. We need to recognize that hypertonus may occur with the use of any oxytocic drug. It is unproductive to defend one drug over another simply because one causes no more hypertonus than the other. It might be more reasonable to suppose that no fetus in utero has ever benefited particularly from any episode of hypercontractility.

Part of the appeal of orally administered PGE_2 for labor induction resides in the fact that it seems to promise an opportunity of getting away from the expensive, somewhat cumbersome equipment and the tedious procedure which have come to be deemed necessary for induction of labor by intravenous oxytocin. Yet the fact is that the method by which oxytocin is applied intravenously is the result of more than 30 years of research and experience during which the physiology of labor has been explored, the relationship of oxytocin to uterine contractility has been elucidated, and the physiologic dose range of oxytocin has been determined. It has been repeatedly demonstrated that the myometrium at term becomes exquisitely sensitive to oxytocin and its proper administration can result in fairly precise control of uterine contractility. There is no indication as yet that prostaglandin administered by any route can achieve the same minute-by-minute control of uterine contractility as can be done with intravenously administered oxytocin. The exact degree of safety of induction of labor by oral PGE_2 needs to be confirmed by its successful use in many more thousands of cases. At any rate, there is absolutely no evidence to date that labor induced by oral PGE_2 is *safer* than is labor induced by intravenous oxytocin.

The current feeling in many institutions is that, for the induction of labor by intravenous oxytocin, not only should a physician be physically present during the induction but labor should be monitored continuously by electronic devices. Since there is no evidence that PGE_2 is capable of inducing labor more safely than oxytocin, one must presume that if labor should be electronically monitored for an intravenous oxytocin induction, it should also be electronically monitored for labor induced by oral PGE_2.

These comments are in no way directed against the concept of labor induction nor against the utilization of either oxytocin or PGE_2 in bringing it about. The ability to induce labor is one of the most valuable and potentially beneficial practices available to the skilled obstetrician. I do believe that we should continue to examine critically the results we are obtaining with our current practices even as we are cautiously striving to improve the technology for its performance.

REFERENCES

1. Liggins, G. C., and Short, R.: Unpublished data, personal communication.
2. Karim, S. M. M., and Sharma, S. D.: Oral administration of prostaglandin E_2 for the induction and acceleration of labor, J. Reprod. Med. **9:** 346, 1972.
3. Friedman, E. A., and Sachtleben, M. R.: Oral prostaglandin E_2 for induction of labor at term, Obstet. Gynecol. **43:** 178, 1974.



Dynafrost tm

BRINGS SPACE AGE MICRO-VALVE TECHNOLOGY TO CRYOSURGERY AT DOWN-TO-EARTH PRICES

Dynatech responded to your needs with this major advance in cryosurgical instrumentation. The DYNAFROST utilizes revolutionary micro-valve technology* to bring you a compact, lightweight instrument with all controls integral to the probe. Just a flick of your thumb to freeze, defrost or shut off, precisely. The slim probe allows maximum visibility. A full complement of tips is available, interchangeable with other Dynatech models.

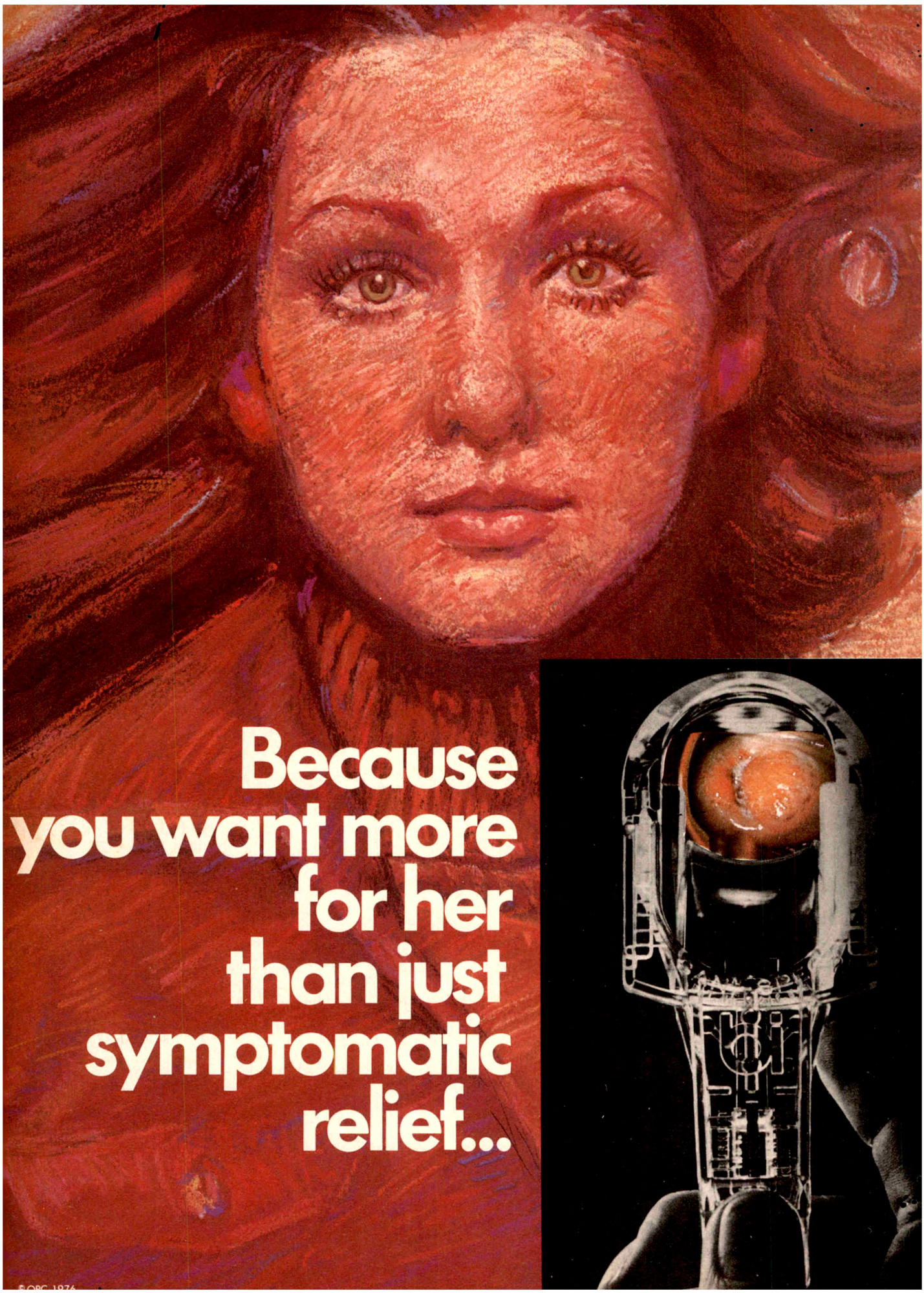
Thoroughly field tested, and manufactured under a new, rigorous program of quality control, the DYNAFROST is so reliable it carries a TWO YEAR WARRANTY. A new safety hose adds to your peace of mind, and the DYNAFROST is more efficient, completes more procedures per tank of CO_2 or N_2O than ever before.

And, the DYNAFROST is unmatched for value. Complete with your choice of four tips — $750!

Write or call today for more information or to arrange a demonstration by your nearby Dynatech representative.

*Patent Applied For.

DYNATECH CRYOMEDICAL COMPANY
90 CAMBRIDGE STREET, BURLINGTON, MASSACHUSETTS, U.S.A. 01803 TEL: (617) 272-6050 TELEX: 94-9461


Because
you want more
for her
than just
symptomatic
relief...

Sultrin
TRADEMARK

Triple Sulfa Cream/Vaginal Tablets

effective against and specific for H. vaginalis

The cause of over 90% of "nonspecific" vaginitis†

effective

based on review by the National Academy of Sciences/National Research Counsel, Sultrin was rated as "effective" against *H. vaginalis.*

prompt symptomatic relief

often within a few days, patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

versatile adjunct in other vaginitides

Sultrin is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

convenient choice of dosage forms

Sultrin comes as a soothing, non-staining and esthetically pleasing cream or convenient vaginal tablets.

Composition: Each SULTRIN Tablet contains sulfathiazole 172.5 mg, sulfacetamide 143.75 mg, and sulfabenzamide 184.0 mg. SULTRIN Triple Sulfa Cream contains sulfathiazole 3.42%, sulfacetamide 2.86%, sulfabenzamide 3.7% and urea 0.64%.
Indications: SULTRIN Tablets and Cream are indicated for treatment of *Haemophilus vaginalis* vaginitis. They may also be used as a deodorant for saprophytic infection following radiation therapy.
Contraindications: Sulfonamide sensitivity and kidney disease.
Dosage: SULTRIN Tablets: One tablet intravaginally before retiring and again in the morning for ten days. This course may be repeated if necessary. SULTRIN Cream: One applicatorful intravaginally twice daily for 4 to 6 days. The dosage may then be reduced one-half to one-quarter.
Supplied: SULTRIN Tablets are available in packages of 20 foil-wrapped tablets with vaginal applicator. SULTRIN Cream is available in 2.75 oz. (78 g) tubes with the ORTHO* Measured-Dose Applicator. OJ 10-6 *TRADEMARK

† Gardner, H.L. and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869


On the OB/GYN service
Mixed infection* may not require "mixed therapy"
for anaerobic infection
for gram-negative aerobic infection
*due to susceptible strains of indicated organisms

GEOPEN® IM/IV

(DISODIUM CARBENICILLIN)

1-gm, 2-gm, 5-gm, and 10-gm vials

for treatment of infections due to anaerobes* and gram-negative aerobes* with *one* antibiotic

*susceptible strains of indicated organisms

Indications: Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa, Proteus* species (particularly indole-positive strains), and certain *Escherichia coli.* Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Severe systemic infections and septicemia, including meningitis due to *Hemophilus influenzae;* genitourinary tract infections including those due to *Neisseria gonorrhoeae, Enterobacter,* and *Streptococcus faecalis* (enterococcus); acute and chronic respiratory infections (though clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft-tissue infections. Also indicated in the following infections due to susceptible anaerobic bacteria: Septicemia; lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis; skin and soft-tissue infections.

Although indicated primarily in gram-negative infections, activity against gram-positive organisms should be kept in mind when both gram-positive and gram-negative organisms are isolated (see **Actions**).

In infections due to certain susceptible strains of *Ps. aeruginosa,* clinical efficacy may be enhanced by combined therapy with gentamicin sulfate in full therapeutic dosages (see gentamicin sulfate package insert).

NOTE: During therapy sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms.

Actions: Organisms found to be susceptible *in vitro* include: GRAM-NEGATIVE ORGANISMS—*Ps. aeruginosa, Proteus mirabilis, Pr. morgani, Pr. rettgeri, Pr. vulgaris, E. coli, Enterobacter* spp, *Salmonella* spp, *H. influenzae, Neisseria* spp, *Bacteroides* spp, and *Fusobacterium* spp.

GRAM-POSITIVE ORGANISMS—*Staphylococcus aureus* (non-penicillinase producing), *Staph. albus, Diplococcus pneumoniae,* beta-hemolytic streptococci, *Str. faecalis, Clostridium* spp, *Peptococcus* spp, and *Peptostreptococcus* spp.

In vitro synergism between Geopen and gentamicin sulfate has been demonstrated for certain strains of *Ps. aeruginosa.*

Some newly emerging pathogenic strains of *Herellea, Mima, Citrobacter,* and *Serratia* have also shown *in vitro* susceptibility.

Not stable in the presence of penicillinase. Most *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly.

Contraindications: Known penicillin allergy.

Warnings: Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations; if bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy.

Individuals with history of penicillin hypersensitivity reactions have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of carbenicillin therapy considered, unless the infection is life threatening and only amenable to carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

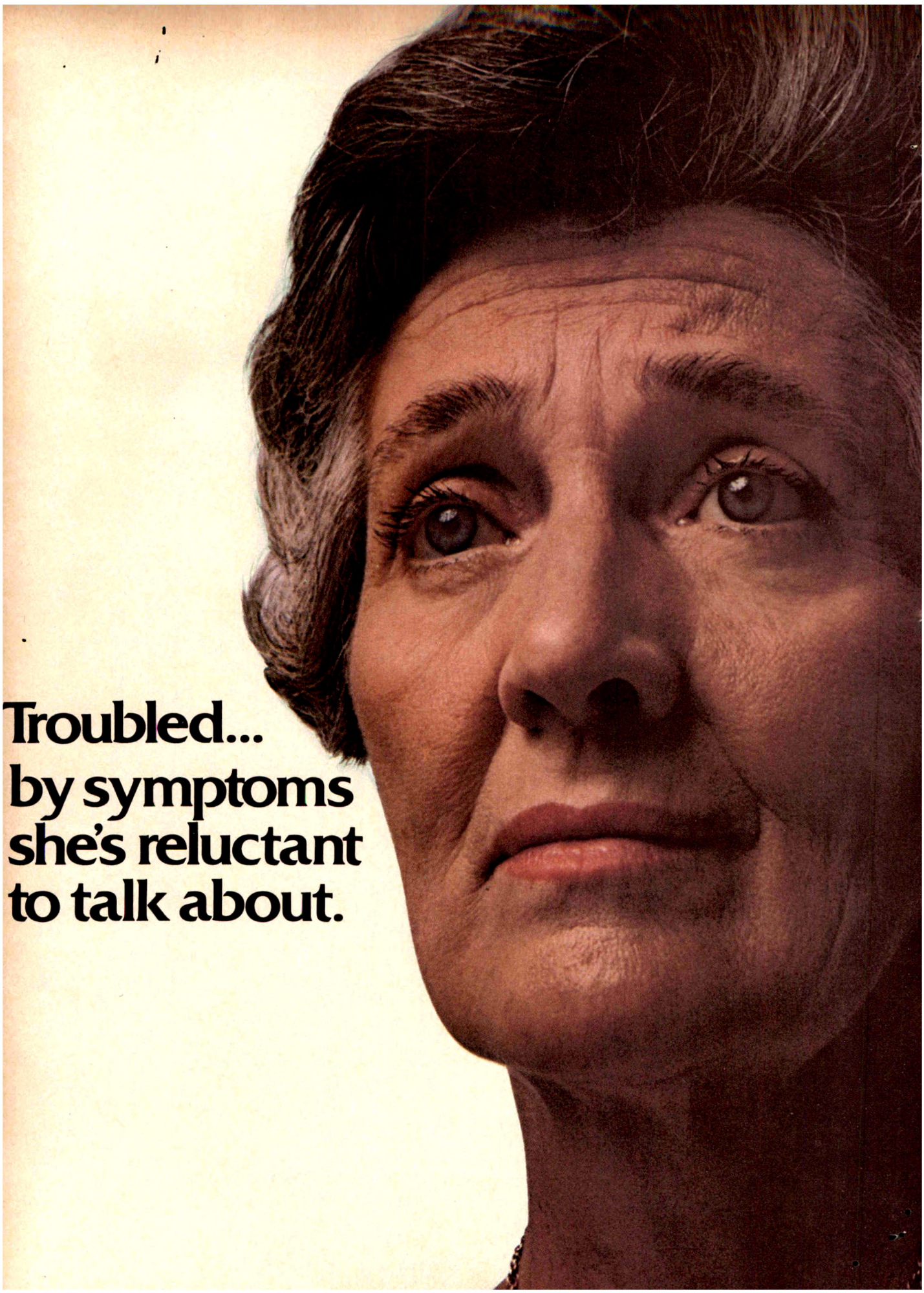
Precautions: As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* spp and *Serratia* spp, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. In a few patients receiving high doses, hypokalemia has been reported; periodic serum potassium determinations should be made and corrective measures should be implemented when necessary. As with any penicillin preparation, an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. Cases of gonorrhea with a suspected primary lesion of syphilis should have darkfield examinations before treatment. In all other cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

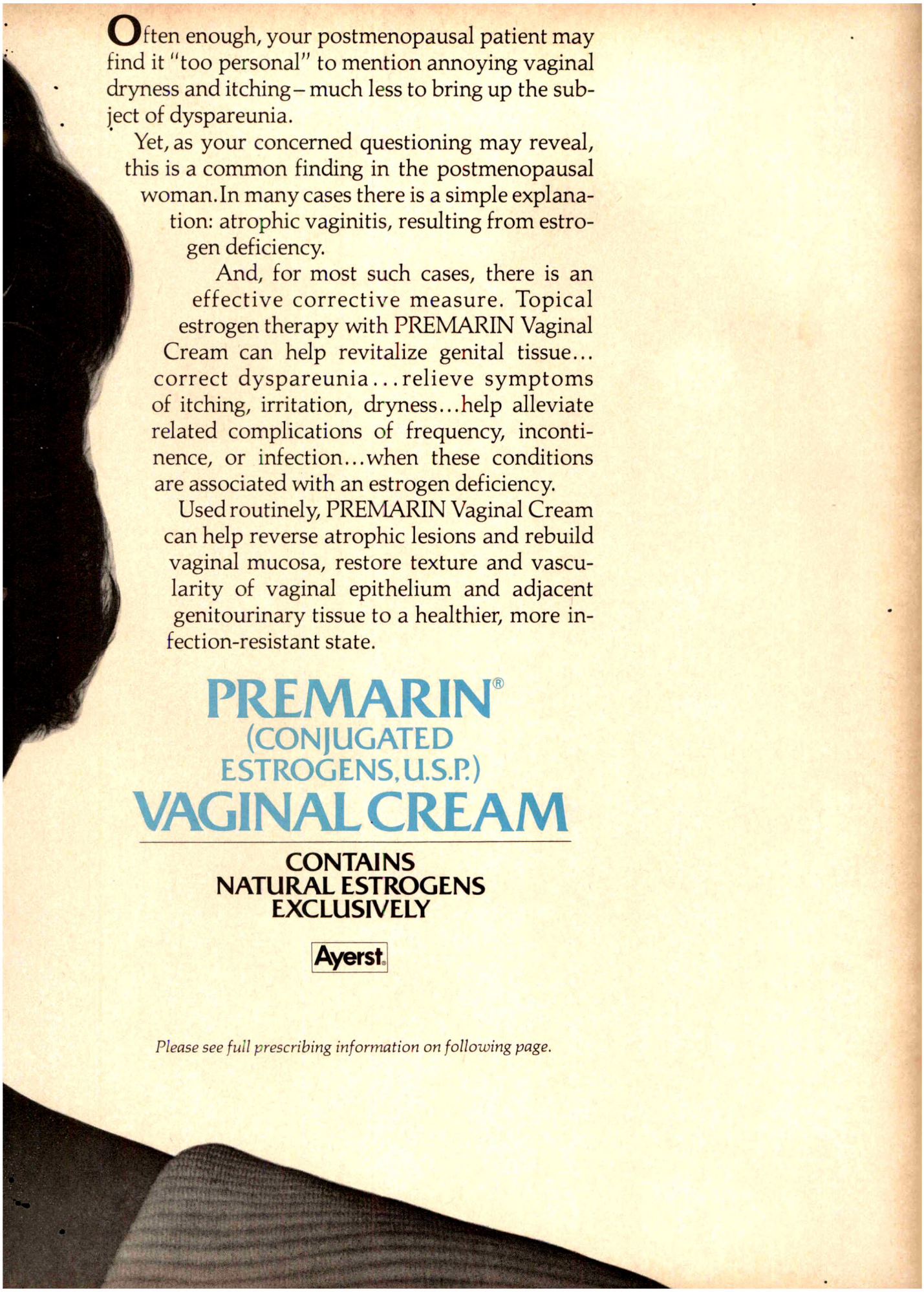
Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. Intravenous infusion should be given as slowly as possible. Reconstituted solution should be discarded after 24 hours if stored at room temperature, after 72 hours if refrigerated. The maximum recommended dose is 40 gm per day; intramuscular injections should not exceed 2 gm per injection.



Adverse Reactions: *Hypersensitivity Reactions*—Skin rashes, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*—Nausea. *Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia. *Blood, Hepatic, and Renal Studies*—SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of hepatic or renal disorders have been demonstrated. *CNS*—Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Other*—Pain at the site of injection, rarely accompanied by induration; in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Vein Irritation and Phlebitis*—Particularly when undiluted solution is injected directly into the vein.

How Supplied: Available in 1-gm, 2-gm, 5-gm, and 10-gm vials. *Before prescribing or administering, see package circular or PDR.*


Troubled...
by symptoms
she's reluctant
to talk about.



Often enough, your postmenopausal patient may find it "too personal" to mention annoying vaginal dryness and itching – much less to bring up the subject of dyspareunia.

Yet, as your concerned questioning may reveal, this is a common finding in the postmenopausal woman. In many cases there is a simple explanation: atrophic vaginitis, resulting from estrogen deficiency.

And, for most such cases, there is an effective corrective measure. Topical estrogen therapy with PREMARIN Vaginal Cream can help revitalize genital tissue... correct dyspareunia...relieve symptoms of itching, irritation, dryness...help alleviate related complications of frequency, incontinence, or infection...when these conditions are associated with an estrogen deficiency.

Used routinely, PREMARIN Vaginal Cream can help reverse atrophic lesions and rebuild vaginal mucosa, restore texture and vascularity of vaginal epithelium and adjacent genitourinary tissue to a healthier, more infection-resistant state.

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.)
VAGINAL CREAM

CONTAINS NATURAL ESTROGENS EXCLUSIVELY

Ayerst®

Please see full prescribing information on following page.

(Complete text of package circular.)

PREMARIN® Vaginal Cream
(CONJUGATED ESTROGENS, U.S.P.)
in a nonliquefying base

DESCRIPTION: Each gram contains 0.625 mg Conjugated Estrogens, U.S.P., in a nonliquefying base.

PREMARIN (Conjugated Estrogens, U.S.P.) is a mixture of estrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 α-dihydroequilin, together with smaller amounts of 17 α-estradiol, equilenin, and 17 α-dihydroequilenin as salts of their sulfate esters.

ACTION: PREMARIN Vaginal Cream provides the local estrogenic activity of topical estrogen.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than nonusers to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients.

Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued.

It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

INDICATIONS: PREMARIN Vaginal Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

CONTRAINDICATIONS: PREMARIN Vaginal Cream is contraindicated in: Patients hypersensitive to its ingredients.

Patients with markedly impaired liver function.

Patients with known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible.

Patients with known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium.

Undiagnosed abnormal genital bleeding.

Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or with a past history of these conditions.

WARNINGS: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately.

Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, the effect of estrogen medication should be stopped.

A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

PRECAUTIONS: Diagnostic measures should be taken to eliminate the possibility of neoplasia or gonorrhea.

The use of PREMARIN Vaginal Cream does not preclude the use of appropriate antimicrobial therapy in the presence of trichomonal, monilial, or bacterial infection.

Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.

Because of estrogen-induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution.

Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely.

Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

A pretreatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals.

When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females.

Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months.

Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

ADVERSE REACTIONS: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis; pulmonary embolism; cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following reactions: coronary thrombosis; neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis).

The following adverse reactions are known to occur in patients receiving estrogens: nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting or withdrawal bleeding; breast tenderness and enlargement; change in body weight (increase or decrease); headache; increased cervical mucus; allergic rash; reactivation of endometriosis; aggravation of migraine headaches; hepatic cutaneous porphyria becoming manifest; cholestatic jaundice; rise in blood pressure in susceptible individuals; mental depression; cystitis-like syndrome; loss of scalp hair; erythema nodosum; hemorrhagic eruption; premenstrual-like syndrome; changes in libido; changes in appetite; nervousness; dizziness; fatigue; backache; erythema multiforme; itching; possible diminution in lactation when given immediately postpartum; irritability; malaise.

DOSAGE AND ADMINISTRATION: *Usual dosage:* Intravaginally or topically, 2 to 4 g daily, depending on the severity of the condition. In postmenopausal surgery, therapy is suggested 10 days before and 10 days following intervention.

HOW SUPPLIED: No. 872—PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains spermaceti, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz (42.5 g) tube.

REFERENCES: 1. Royal College of General Practitioners: Oral contraception and thrombo-embolic disease, J. Coll. Gen. Pract. *13*:267, 1967. 2. Inman, W.H.W., and Vessey, M.P.: Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age, Br. Med. J. *2*:193, 1968. 3. Vessey, M.P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report, Br. Med. J. *2*:651, 1969. 4 Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E.: Thromboembolism and oral contraceptives: An epidemiological case-control study, Am. J. Epidemiol. *90*:365 (Nov) 1969. 5. Inman, W.H.W., Vessey, M.P., Westerholm, B., and Engelund, A.: Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs, Br. Med. J. *2*:203, 1970. 6. Herbst, A.L., Ulfelder, H., and Poskanzer, D.C.: Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women, N. Engl. J. Med. *284*:878 (Apr. 22) 1971.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

7648

A standard of fetal growth for the United States of America

WILLIAM E. BRENNER, M.D.
DAVID A. EDELMAN, PH.D.
CHARLES H. HENDRICKS, M.D.
Chapel Hill and Research Triangle Park, North Carolina

The appropriate interpretation of monitored fetal growth throughout pregnancy in individual patients and populations is dependent upon the availability of adequate standards. There is no adequate standard of fetal weight throughout pregnancy that is suitable for patients in the U. S. A. To determine such a standard for infants delivered at about sea level the 10th, 25th, 50th, 75th, and 90th percentiles of fetal weight for each menstrual week of gestation were calculated from 430 fetuses at 8 to 20 menstrual weeks' gestation aborted with prostaglandins and from 30,772 liveborn infants delivered of patients at 21 to 44 menstrual weeks' gestation. Median fetal crown-to-rump lengths and crown-to-heel lengths were derived from measurements of 496 aborted fetuses of 8 to 21 weeks' gestation. Fetal weight correction factors for parity, race (socioeconomic status), and fetal sex were calculated. The derived fetal growth curves are useful for clinical, public health, and investigational purposes. (AM. J. OBSTET. GYNECOL. 126: 555, 1976.)

WITH THE ADVENT of new monitoring techniques, fetal and maternal condition can be better evaluated throughout pregnancy. Although assessment of fetal growth is an important aspect of fetal monitoring, the expected ranges of fetal weight and growth throughout pregnancy have not been adequately determined. Accurate knowledge of fetal growth is clinically important for at least three reasons: (1) to identify the effects of pathologic pregnancies on fetal size, (2) to aid in the evaluation of diagnostic measurements of fetal growth, and (3) to identify potentially abnormal children in the antepartum or immediately postpartum periods.

From the Department of Obstetrics and Gynecology, University of North Carolina, and the International Fertility Research Program.

This work was supported in part by the National Institutes of Health, United States Public Health Service (Grant H.E. 01914-09), the International Fertility Research Program at Chapel Hill (AID/csd 2979), and by the Public Health Research Grant RR-46 for the General Clinical Research Center's Branch of the Division of Research Resources. Prostaglandin was supplied by the Upjohn Company, Kalamazoo, Michigan.

Presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. William E. Brenner, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina 27514.

Available data on fetal size and growth throughout pregnancy are not adequate for many clinical purposes. Streeter[1] conducted the most comprehensive study of embryo and fetal growth in early pregnancy and reported values for formalin-fixed and embalmed specimens. Although his measurements of sitting height, head size, and head-to-foot length are similar to those of nonpreserved specimens, fetal weights differ significantly. Since the weight change caused by formalin is dependent upon several factors, there is no reliable way to determine the weight of the nonpreserved from the preserved fetus.

Fetal weight and some of the parameters that appear to be associated with differential rates of fetal growth in the latter part of the second trimester and throughout the third thrimester in specific patient populations have been reported by several investigators. Unfortunately, either these studies pertain to selected populations who are not representative of all subgroups in the U. S. A. or the studies are too small to permit accurate determination of fetal growth percentiles. The importance of evaluating the relationships between fetal growth and such variables as fetal sex, and maternal race, socioeconomic factors, and parity has been previously reported.[2, 3]

One of the most frequently used standards of fetal growth is the one reported by Lubchenco and associ-

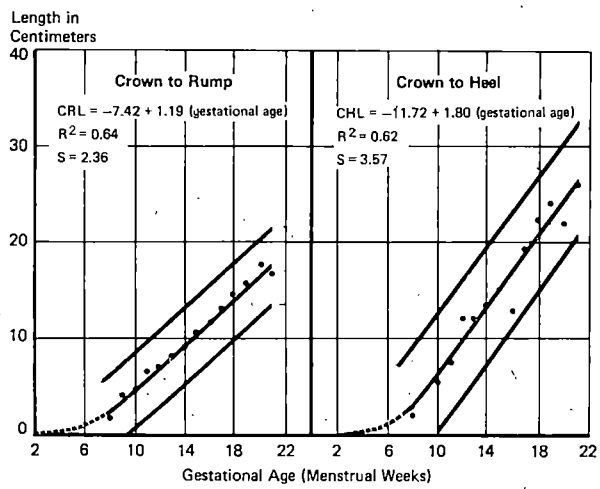


Fig. 1. Fetal length: left, crown-to-rump; right, crown-to-heel. Regression of crown-to-rump length *(CRL)* and crown-to-heel length *(CHL)* with 90 per cent confidence limits on a future CRL and CHL are graphed from data derived from 496 prostaglandin-induced abortions. Each dot represents the mean CRL and CHL for a given gestational age, *(S)* is the estimated standard deviation about the regression line, (R^2) is the multiple correlation coefficient, and the dashed line is an extrapolation to 0 cm. at 2 menstrual weeks' gestation.

Table I. Selected patient characteristics

8-21 weeks' gestation			*21-44 weeks' gestation*		
Characteristic	*No.*	*%*	*Characteristic*	*No.*	*%*
Age (yr.):			*Age (yr.):*		
20	169	34.1	20	6,216	20.2
20-29	297	59.9	20-29	17,755	57.7
30-39	27	5.4	30-39	6,401	20.8
40+	3	0.6	40	400	1.3
Parity:			*Parity:*		
0	280	56.4	1	10,032	32.6
1-2	168	33.9	2	7,836	25.5
3-4	41	8.3	3-4	8,893	28.9
5+	7	1.4	5+	4,009	13.0
Race:			*Race:*		
White	252	50.8	White	16,401	53.3
			Private	15,077	49.0
			Staff	1,324	4.3
Non-white	244	49.2	Nonwhite	14,371	46.7
			Private	1,723	5.6
			Staff	12,648	41.1

ates,[4] derived from deliveries at 24 to 42 menstrual weeks' gestation. Their study was based on relatively few (5,635) selected infants born to Caucasian mothers of low socioeconomic status at a high elevation (5,280 feet). Their derived fetal growth rates may be inappropriate for other areas of the United States, since fetal growth may be affected by altitude, and these other areas may have populations with different races, socioeconomic, and parity compositions. Fetal growth standards for the past generations,[5] for other countries,[6–12] and for other specific U. S. A. groups[13–15] may not be representative of present-day fetal growth standards in the U. S. A.

To determine the "normal" (expected) range of fetal weight throughout pregnancy at sea level for most U. S. A. patient types, the association of selected variables with fetal weight and fetal length in early pregnancy, pertinent data from 31,268 prostaglandin-induced abortions and deliveries after spontaneous labor at 8 to 44 menstrual weeks' gestation were analyzed.

Materials and methods

To determine fetal growth from 8 to 21 menstrual weeks' gestation, 641 fetuses aborted with prostaglandins (PG's) were weighed and measured. All abortions were legally approved and performed in the Clinical Research Unit of the Memorial Hospital, University of North Carolina at Chapel Hill (elevation 513 feet), during the period of 1972 to 1975. Abortions were induced with PG's according to investigational protocols; $PGF_{2\alpha}$ by the intra-amniotic and vaginal routes, PGE_2 by the vaginal route, 15(S)-15-methyl $PGF_{2\alpha}$ by the intra-amniotic and intramuscular routes, and 15(S)-15-methyl PGE_2 by the intramuscular route. Neither the systemic nor intrauterine administration of any of these prostaglandins is known to cause effects in the fetus that would change either its weight or size. Fetal weights and crown-to-rump and crown-to-heel lengths from intact fetuses were obtained within 30 minutes of delivery with a Mettler electronic scale and ruler.

Gestational age for the abortions was "estimated" by a combination of the physician's estimate based on uterine size and the patient's stated last normal menstrual period (LNMP). Neither of the two estimates of gestional age alone was satisfactory. Therefore, only data from 496 of the 641 pregnancies where the LNMP estimate and the physician's estimate of gestional age differed by no more than 2 weeks were analyzed for fetal length. Fetal weights were derived from 430 fetuses at 8 to 20 weeks' gestation.

Fetal weight from 21 to 44 menstrual weeks' gestation was determined with the use of data from 30,772 deliveries during the period from 1962 to 1969 at MacDonald House, University Hospitals of Cleveland, Ohio (elevation 660 feet). Data were analyzed from single births with the infant living at the onset of labor among pregancies not complicated by pre-eclampsia, breech, erythroblastosis, diabetes mellitus, or congenital abnormalities. Subsets of some of these data have been previously reported.[2, 3, 16, 17] Gestational age was calculated to the nearest week of gestation from the

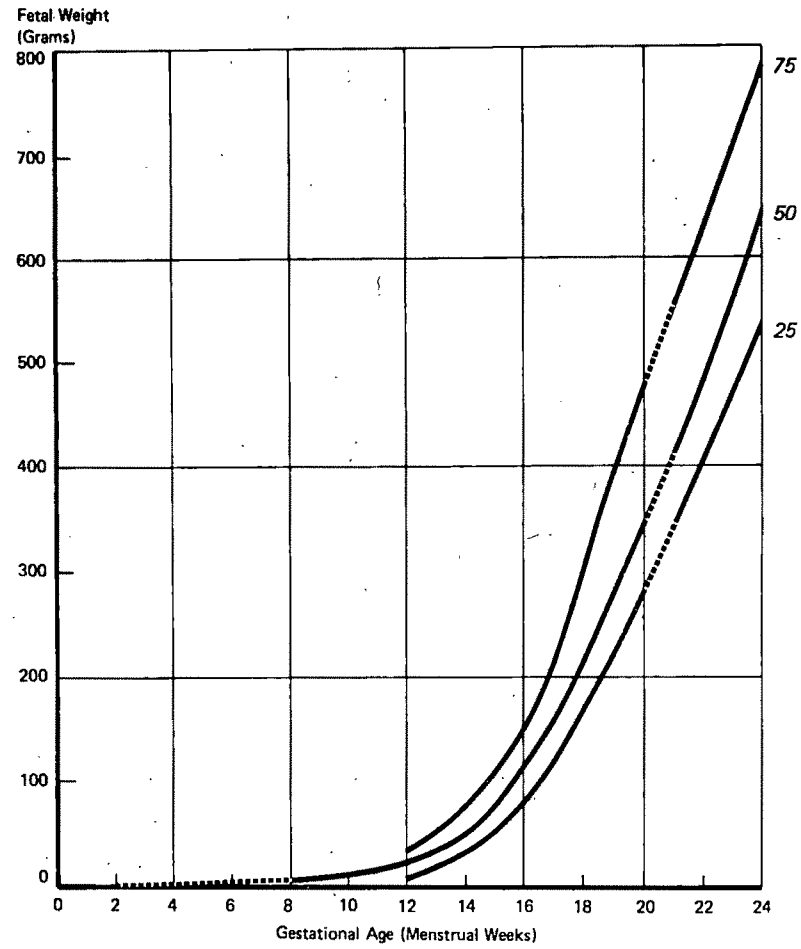


Fig. 2. Fetal weight during early pregnancy. The 50th (median), 25th, and 75th percentiles of fetal weight in grams during the initial 24 menstrual weeks of pregnancy as calculated from 430 prostaglandin-induced abortions at ≤20 weeks' and 30,772 "spontaneous" deliveries from 21 to 44 weeks' gestation are graphed. Dashed lines are extrapolations between the data sets and to 0 Gm. at 2 menstrual weeks' gestation.

patient's LNMP. Infants were weighed on a balance scale immediately after delivery.

Fetal weight percentiles were calculated from the data at each week of gestation. The resulting 10th, 25th, 50th, 75th, and 90th percentile curves for fetal weight were then smoothed with two-point weighted means. Simple linear regression techniques were used for the analyses of crown-to-heel and crow-to-rump lengths. Whenever statistical tests were used, only the p value—the significance level of the test—is presented.

Subjects. Although the race distribution for patients in the 8 to 21 week group was similar to that of those in the 21 to 44 week group, the distributions of age and parity differed (Table I). In both groups 98 per cent of the nonwhite patients were blacks. Patients in the 21 to 44 weeks' group were classified as staff or private, depending on their ability to pay private physician costs, whereas patients in the 8 to 21 weeks' group were not so classified. Since 90.5 per cent of the staff patients were nonwhite and 89.7 per cent of the private patients were white, the effects of these two variables, race and socioeconomic status, on fetal growth could not be adequately separated.

Results

Fetal length (8 to 21 weeks' gestation). The relationship of both crown-to-rump (CRL) and crown-to-heel (CHL) lengths to gestational age appears to be linear during this period of gestation (Fig. 1). The calculated regressions of the CRL and CHL on gestational age are given by:

CRL = −7.42 + 1.19 (gestational age) s = 2.36 cm.
CHL = −11.72 + 1.80 (gestational age) s = 3.57 cm.

In the range of 8 to 21 menstrual weeks' gestation the expected CRL and CHL are calculated from the

Table II. Fetal weight percentiles throughout pregnancy

Gestational age (menstrual weeks)	*No. of women*	*Smoothed percentiles*				
		10	*25*	*50*	*75*	*90*
8	6	—	—	6.1*	—	—
9	7	—	—	7.3*	—	—
10	15	—	—	8.1*	—	—
11	13	—	—	11.9*	—	—
12	18	—	11.1	21.1	34.1	—
13	43	—	22.5	35.3	55.4	—
14	61	—	34.5	51.4	76.8	—
15	63	—	51.0	76.7	108	—
16	59	—	79.8	117	151	—
17	36	—	125	166	212	—
18	58	—	172	220	298	—
19	31	—	217	283	394	—
20	21	—	255	325	460	—
21	43	280	330	410	570	860
22	69	320	410	480	630	920
23	71	370	460	550	690	990
24	74	420	530	640	780	1,080
25	48	490	630	740	890	1,180
26	86	570	730	860	1,020	1,320
27	76	660	840	990	1,160	1,470
28	91	770	980	1,150	1,350	1,660
29	88	890	1,100	1,310	1,530	1,890
30	128	1,030	1,260	1,460	1,710	2,100
31	113	1,180	1,410	1,630	1,880	2,290
32	210	1,310	1,570	1,810	2,090	2,500
33	242	1,480	1,720	2,010	2,280	2,690
34	373	1,670	1,910	2,220	2,510	2,880
35	492	1,870	2,130	2,430	2,730	3,090
36	1,085	2,190	2,470	2,650	2,950	3,290
37	1,798	2,310	2,580	2,870	3,160	3,470
38	3,908	2,510	2,770	3,030	3,320	3,610
39	5,413	2,680	2,910	3,170	3,470	3,750
40	10,586	2,750	3,010	3,280	3,590	3,870
41	3,399	2,800	3,070	3,360	3,680	3,980
42	1,725	2,830	3,110	3,410	3,740	4,060
43	507	2,840	3,110	3,420	3,780	4,100
44	147	2,790	3,050	3,390	3,770	4,110

*Median fetal weights may be overestimated. They were derived from only a small proportion of the fetuses delivered at these weeks' gestation.

above equations. The 95 per cent confidence limits on a future CRL or CHL for gestations over 10 weeks are approximated by the expected CRL ±3.9 cm. and by the expected CHL ±6.0 cm. The relationship of fetal length to age is curvilinear in the very early pregnancy.

Fetal weight. The 25th, 50th, and 75th percentiles of fetal weight during the initial 24 weeks' gestation are portrayed in Fig. 2. The continuity of the percentiles of the two data sets [(1) abortions at Chapel Hill and (2) neonates at Cleveland] is apparent.

The 10th, 25th, 50th, 75th, and 90th percentiles of fetal weight throughout pregnancy are portrayed in Fig. 3 and detailed in Table II. These percentiles are not adjusted for fetal sex or maternal parity and race.

Growth rate expressed as the median fetal weight gain per week increased progressively until 34 to 36 weeks' gestation, after which the weekly fetal weight increment decreased (Fig. 4). In contrast, when growth rate (weight gain) is expressed as the percentage increase in weight over the previous week, the maximum percentage increase in weight is in early pregnancy and progressively decreases throughout pregnancy (Fig. 5).

Variables associated with differences in fetal weight. Maternal parity and race (socioeconomic) and fetal sex are associated with significant ($p < 0.10$) differences in median fetal weights in the latter part of pregnancy (Fig. 6). After 34 to 38 weeks' gestation, median fetal weights were significantly different (p

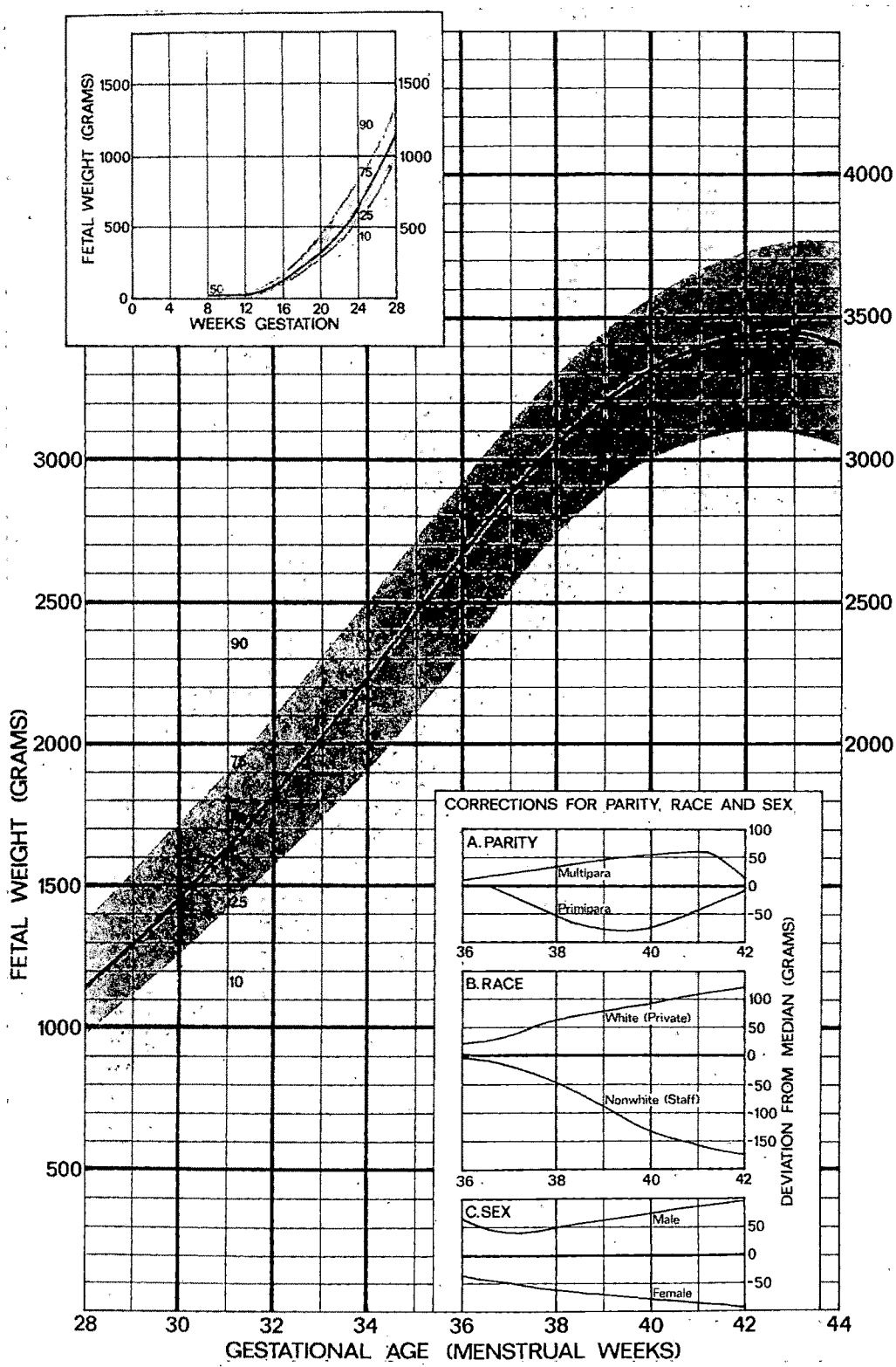


Fig. 3. Fetal weight. The 50th (median), 10th, 25th, 75th, and 90th percentiles of fetal weight in grams throughout pregnancy and correction factors for parity, race (socioeconomic), and sex derived from 31,202 prostaglandin-induced abortions and "spontaneous" deliveries are graphed.

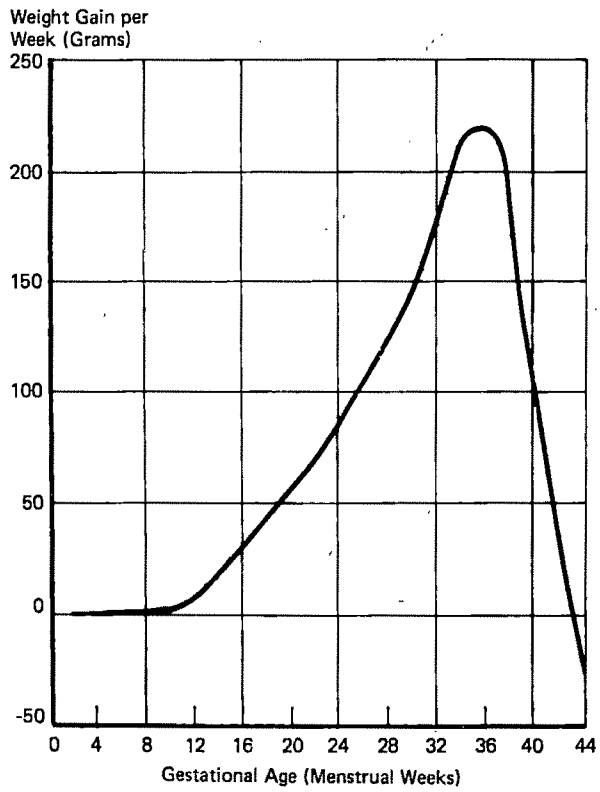


Fig. 4. Weekly fetal weight gain throughout pregnancy. The median weight gain in grams each week throughout pregnancy among 31,202 prostaglandin-induced abortions and "spontaneous" deliveries are graphed.

<0.10) for primiparas and multiparas, for whites (private) and nonwhites (staff), and for male and female fetuses. Distributions of fetal weights about the median weights at each week after the 34th week for each of the above variables were similar. Before 34 weeks' gestation, median fetal weights were not significantly different ($p > 0.10$) for these variables.

At each gestational age after 36 weeks' the median weights were plotted in Fig. 6 and deviations from the median were plotted in Fig. 3 for patients of different parities and races (socioeconomic) and fetal sexes. Analyses indicated that the effects of these variables on median fetal weight could be considered additive. From Fig. 3 the expected fetal weight (EFW) adjusted for sex, and/or parity, and/or race (socioeconomic) can be determined within ±50 grams. For a selected maternal gestational age the adjustment is made by adding to the median fetal weight the grams' deviation for the effects of sex, parity, and race (socioeconomic). For example, the expected fetal weight (EFW) for a singleton delivery to a white private primigravid patient at 39 weeks' gestation is obtained by adding to the uncorrected median weight for 39 weeks' gestation (3,170 grams) the correction factors at 39 weeks' for primigravidas (−65 grams) and for white patients (private (+75 grams) [EFW = 3,170 − 65 + 75 = 3,180 grams]. If the fetal sex is known, the EFW can be further adjusted by adding the fetal sex correction factor.

Comment

A U. S. A. standard of fetal weight throughout pregnancy for singleton uncomplicated pregnancies delivered at about sea level has been determined for male and female fetuses, nulliparas, and multiparas and for whites and nonwhites. Although median weight of specific U. S. A. populations may vary from these medians, with appropriate corrections for sex, parity, and race, the derived median fetal weights at each gestational age will probably be accurate enough for clinical and investigational purposes. Other variables such as maternal smoking habits, diseases, abnormal presentations, nutrition, and addictions which may affect fetal weight were not evaluated in this study. It was the objective of this study to evaluate fetal growth for "normal" pregnancies rather than for pathologic and nutritional conditions and personal habits that may be altered and/or may depend upon local conditions.

The validity of using fetal weights from deliveries after spontaneous labor ("spontaneous" deliveries) during the late second and early third trimesters had been questioned, since a large proportion of these pregnancies may have been abnormal and resulted in fetal weights that are not representative of "normal" growth. Because there was good continuity in the fetal weight percentile curves derived from prostaglandin-induced abortions and from fetuses born after "spontaneous" labor, it appears that the fetal weight percentiles derived from "spontaneous" deliveries in the late second and third trimesters are valid for interpreting "normal" (usual) fetal growth.

Mean crown-to-rump length (CRL) (sitting height) and crown-to-heel length (CHL) at each week of gestation reported in this study were similar to those previously reported.[1, 18] From 8 to 21 weeks' gestation the relationship to fetal length was linear in all of these studies. In contrast, Haase's rule, a commonly used calculation for determining the expected CHL, yields a curvilinear growth rate during the initial 20 weeks' gestation and a linear relationship thereafter. Haase's rule: The expected CHL in centimeters for the initial five lunar months of pregnancy is determined by dividing the number of menstrual weeks' gestation by four and squaring the quotient; after the fifth lunar month the expected CHL is determined by dividing the number of menstrual weeks' gestation by four and

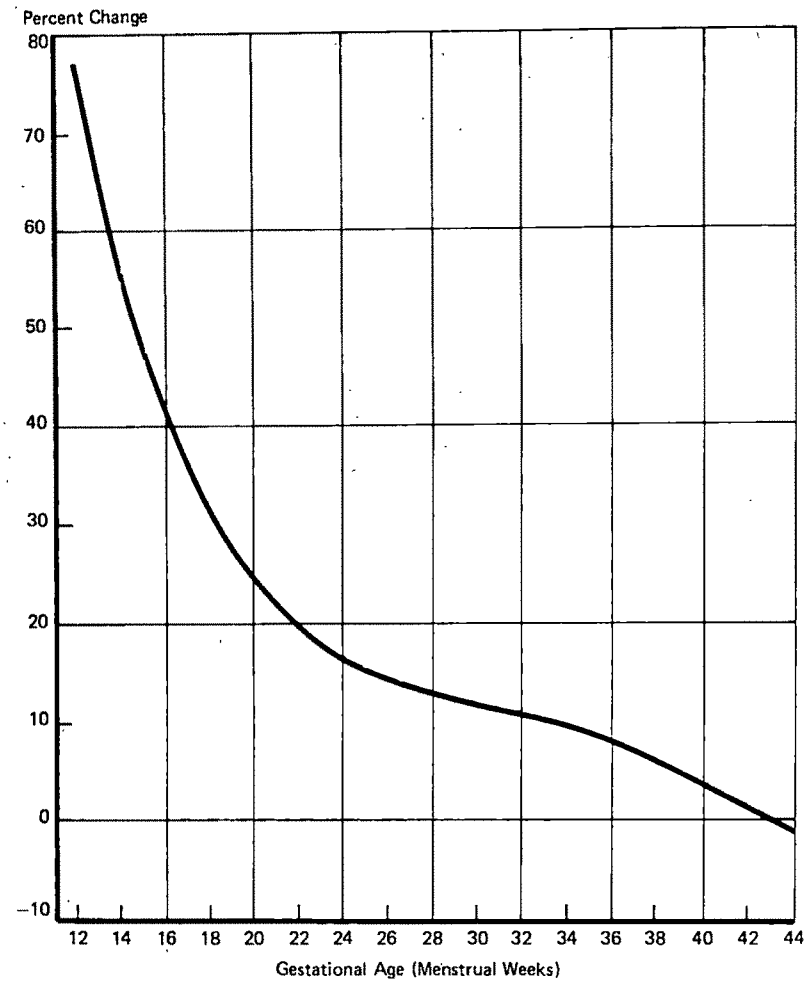


Fig. 5. Percentage increase in weight over previous week throughout pregnancy. Throughout pregnancy, the median percentage increase in fetal weight during the week prior to the plot among 31,202 prostaglandin-induced abortions and "spontaneous" deliveries is graphed.

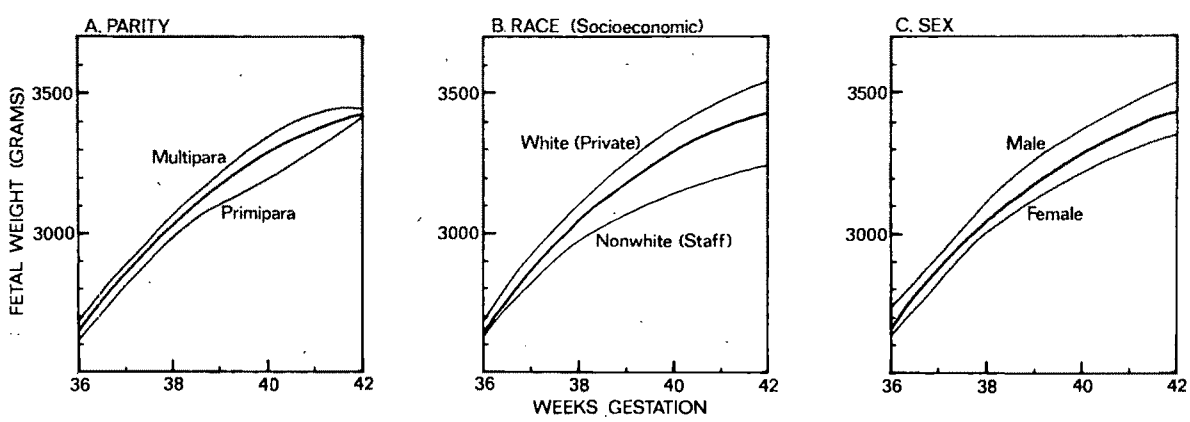


Fig. 6. Median fetal weight by parity, race, (socioeconomic) and sex. The median fetal weight in grams during 36 to 42 menstrual weeks' gestation derived from 31, 202 prostaglandin-induced abortions and "spontaneous" deliveries (central unmarked line) are graphed with fetuses of different sexes and born to mothers of different parities and races (socioeconomic). Deviations prior to 36 weeks' gestation were not significant ($p > 0.10$).

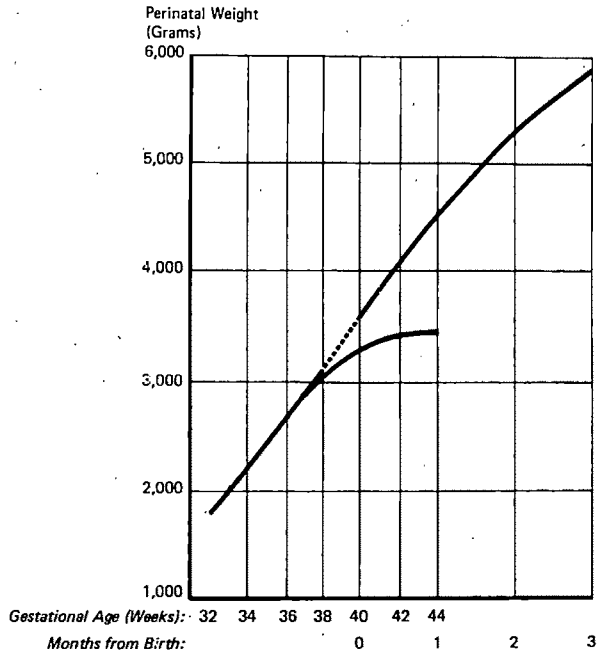


Fig. 7. Median perinatal weight. Graphed are the median weight in grams throughout the latter part of pregnancy derived from 30,772 "spontaneous" deliveries, and the media weight throughout the initial 3 months of life as reported by H. C. Stuart, M.D., and associates.[23] The dashed line is an extrapolation of the best fitting line to indicate similar rates of growth.

multiplying the quotient by five.[19] Although Haase's rule may be useful for rough determinations of expected fetal lengths, it should not be used as a standard for fetal lengths or for determining rates of fetal growth.

Fetal weights for use as clinical standards must be derived from recently delivered, nonmacerated, nonfixed specimens with an accurately determined gestational age. To obtain estimates of fetal size at 8 to 28 weeks' gestation for use by embryologists, Streeter[1] used 704 formalin-fixed or embalmed specimens in different conditions and states of preservation obtained from many sources over a period of several years. The gestational ages were derived by several methods. He derived the estimates of the expected formalin-fixed fetal weight at 28 to 40 weeks' gestation by adding 5 per cent (an estimate of the amount added by embalming) to the mean weights reported by Zangemeister.[5] However, formalin fixing and embalming do not add a consistent amount or percentage of weight and the amount of weight added depends upon several factors.[20] In our study the median weights at each week's gestation were from 0 to 40 grams higher at 14 to 26 weeks' and from 0 to 200 grams higher at 27 to 30 weeks' gestation than those reported by Streeter.[1] Unfortunately, it is not always made clear in textbook presentations that Streeter's data are for the embryologist's use to estimate gestational age from the weight of a fixed specimen and not for clinicians dealing with nonfixed specimens.

Many of the values reported for fetal weight and growth during the latter part of pregnancy are not satisfactory for use in today's U. S. A. population. Fetal weights derived many years ago[5] were lower and therefore are unsatisfactory for today's standards. Median weights in India[6] and Singapore[7] were consistently lower, and those in Sweden,[9] Holland,[8] and Scotland[11] were higher, whereas those reported from Canada,[12] parts of the U. S. A.,[13–15] and Austria[10] were similar to subgroups in this study. National standards change and periodically need revision. Some methods, such as use of birth certificate data and the inclusion of weights of dead fetuses or only fetuses that live throughout the neonatal period, result in inaccurate fetal weight standards.

Standards for fetal weight derived from very specific populations are usually satisfactory for only that population. Among the indigents in Atlanta, Negroes had lower male and female birth weights at each gestational age after 37 weeks' gestation than did Caucasians.[13] The median birth weights of Negroes were similar to only the nonwhite subpopulation in our study. Probably the most frequent standard of fetal weight used in the U. S. A. is the one reported by Lubchenco and associates.[4] Using various "corrections," they reported combined weights of infants born to 5,635 indigent Spanish American patients in Denver, Colorado (elevation 5,280 feet). Their 90th, 50th, and 10th percentile weights after 30 weeks' gestation were about 100 grams less than those reported in our study.

Growth curves are potentially useful for several purposes in the clinical practice of obstetrics and gynecology and pediatrics as well as in public health and the social sciences. Adequate fetal growth standards may be used as a basis for more informed clinical judgments and for better interpretation of the results of fetal monitoring. For example, in complicated pregnancies, when evaluating the best time for delivery, determination of the expected fetal weight at the present gestational age and the expected weight gain with each duration of delay may be helpful. Serial determinations of fetal growth by ultrasound and other methods, if correlated with fetal weight, could be used to assess growth retardation and the effects of different therapies. Although neonates weighing less than 3.5 pounds and/or with "severe intrauterine growth retardation" have higher rates of mortality and atten-

uated somatic, psychological, and intellectual growth as compared to their peers,[21, 22] better definition of the high- and low-risk neonate groups may be possible with the availability of accurate growth standards.

Growth curves may be useful for selecting groups that might benefit from specific public health and educational programs and for partially evaluating the effects of such programs. Nutritional and special educational and psychological adjustment programs for the very premature and severely growth-retarded infants may decrease their mortality rate, improve their psychological adjustment, and promote their maximum somatic and intellectual growth. More appropriate and successful treatment and education programs may be devised if concentrated follow-up programs of high-risk children are created to detect neurological, speech, hearing, eye, and behavior problems. The effects on fetal growth of genetic factors, illnesses, and personal habits such as smoking, diet, and addiction can be evaluated so that potential parents can be counseled and effective public health programs can be initiated. Serial fetal growth rate curves over several years could be used to partially evaluate specific nutritional, medical care, and educational programs.

Large, controlled, long-term comparative studies of various methods of managing pregnancies with intrauterine growth retardation from different causes and at various stages of gestation need to be conducted. The most frequently used method of managing the growth-retarded fetus is either by the continued observation of the pregnancy until spontaneous labor occurs, or by effecting early delivery if there is presumptive evidence that continuation of the pregnancy will permanently injure the mother or there is a high probability that fetal death is imminent. However, there are reasons for believing that this approach rather than earlier delivery and adequate neonatal nutrition may result in less than optimal development in some fetuses.

Reduced intrauterine growth rate is probably associated with suboptimal fetal development. After a transient decrease in fetal growth while adapting to the extrauterine environment, the neonate gains[23] weight at a rate similar to the maximum rate noted during intrauterine development (Fig 7). Intrauterine growth retardation appears frequently to stem from a deficient intrauterine environment rather than an abnormality in the fetus since (1) after birth, low-birth-weight neonates often gain weight at a more rapid rate than their normal or high birth weight peers[24]; (2) the intrauterine growth rate of each fetus in multiple pregnancies is negatively related to the number of fetuses[25]; (3) fetuses of malnourished mothers[3, 26, 27] and/or pre-eclamptic mothers[16] have attenuated growth; and (4) in some populations the maximum rate of fetal growth continues into the latter part of pregnancy.[9]

The anatomical and functional effects of human intrauterine growth retardation are unknown. However, the decreased fetal brain growth that has been reported in animals when there are maternal nutritional deficiencies in the latter part of pregnancy may also occur in some growth-retarded human fetuses.[26, 27] Defects resulting from undernutrition during development may not be repaired even if adequate nutrition is later resumed. Fetuses of undernourished bitches and mice have smaller brains and a decreased number of central nervous system neurons than the offspring of well-nourished animals.[26, 27] This decrease in neurons persists into later life even though there has been good neonatal nutrition.[26, 27] Some investigators believe that this decrease in anatomical growth does not imply a functional deficiency.[28]

Although intrauterine growth retardation results potentially in less than the optimal neurologic and somatic development, the functional deficit may not always be demonstrable by the use of standardized tests for "normal" populations. Although the mean somatic size and intellectual and behavioral ratings of intrauterine growth–retarded infants are within "normal" ranges by 5 years of age, they are consistently less than those of their "peers."[21] Neurological deficiencies stemming from intrauterine growth retardation may not be adequately defined by IQ scores. Of 96 children born with "severe" growth retardation after 38 weeks' gestation, the mean IQ was 95 for males and 101 for females, but 50 per cent of males and 36 per cent of females had "poor" school performance; 59 per cent of males and 69 per cent of females had speech defects; 1 per cent had cerebral palsy; 6 per cent had convulsions; and 25 per cent had evidence of cerebral dysfunction.[22]

In consideration of such findings it appears that delivery of the growth-retarded fetus at a time when there is a high probability of extrauterine survival may result in less permanent damage to the infant than does the present practice of continued observation until there is evidence of maternal danger or impending fetal death. However, appropriate studies will be necessary to determine the best method of managing patients at different gestational ages with different degrees of intrauterine growth retardation from different causes and for managing the growth-retarded neonate.

REFERENCES

1. Streeter, G. L.: Weight, sitting height, head size, foot length, and menstrual age of the human embryo, Contrib. Embryol. **11:** 143, 1920.
2. Hendricks, C. H.: Patterns of fetal and placental growth: The second half of normal pregnancy, Obstet. Gynecol. **24:** 357, 1964.
3. Hendricks, C. H.: Delivery patterns and reproductive efficiency among groups of differing socioeconomic status and ethnic origins, AM. J. OBSTET. GYNECOL. **97:** 608, 1967.
4. Lubchenco, L. O., Hansman, C., Dressler, M., and Boyd, E.: Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks of gestation, Pediatrics **32:** 793, 1963.
5. Zangemeister, W.: Die Altersbestimmung des Fötus nach graphischer methode, Z. Geburtshilfe Gynaekol. **69:** 127, 1911.
6. Pachauri, S., Marwah, S. M., and Rao, N. S. N.: A multifactorial approach to the study of the factors influencing birth weight in the urban community of New Delhi, Indian J. Med. Res. **59:** 1318, 1971.
7. Cheng, M. C. E., Chew, P. C. T., and Ratnam, S. S.: Birthweight distribution of Singapore Chinese, Malay and Indian infants from 34 weeks to 42 weeks gestation, J. Obstet. Gynaecol. Br. Commonw. **79:** 149, 1972.
8. Kloosterman, G. J.: On intrauterine growth. The significance of prenatal care, Int. J. Gynaecol. Obstet. **8:** 895, 1970.
9. Sterky, G.: Swedish standard curves for intra-uterine growth, Pediatrics **46:** 7, 1970.
10. Hohenauer, L.: Intrauterines Längen-und Gewichtswachstum Standardwerte aus Österreich, Pädiatr. Pädol. **8:** 195, 1973.
11. Thomson, A. M., Billewicz, W. Z., and Hytten, F. E.: The assessment of fetal growth, J. Obstet. Gynaecol. Br. Commonw. **75:** 903, 1968.
12. Usher, R., and McLean, F.: Intrauterine growth of liveborn Caucasian infants at sea level: Standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation, Pediatrics **74:** 901, 1969.
13. Freeman, M. G., Graves, W. L., and Thompson, R. L.: Indigent Negro and Caucasian birth weight–gestational age tables, Pediatrics **46:** 9, 1970.
14. Gruenwald, P.: Growth of the human fetus. I. Normal growth and its variation, AM. J. OBSTET. GYNECOL. **94:** 1112, 1966.
15. Babson, S. G., Behrman, R. E., and Lessel, R.: Liveborn birth weights for gestational age of white middle class infants, Pediatrics **45:** 937, 1970.
16. Hendricks, C. H., and Brenner, W. E.: Toxemia of pregnancy: Relationship between fetal weight, fetal survival, and the maternal state, AM. J. OBSTET. GYNECOL. **109:** 225, 1971.
17. Brenner, W. E., Bruce, R. D., and Hendricks, C. H.: The characteristics and perils of breech presentation, AM. J. OBSTET. GYNECOL. **118:** 700, 1974.
18. Berger, G. S., Edelman, D. A., and Kerenyi, T. D.: Fetal crown-rump length and biparietal diameter in the second trimester of pregnancy, AM. J. OBSTET. GYNECOL. **122:** 9, 1975.
19. Haase, W.: Maternity annual report for 1875, Charité Ann. **2:** 669, 1877.
20. Schultz, A. H.: Changes in fetuses due to formalin preservation, Am. J. Phys. Anthropol. **2:** 35-41, 1919.
21. Drillien, C. M.: The growth and development of the prematurely born infant, Baltimore, 1964, The Williams Wilkins Company.
22. Fitzhardinge, P. M., and Steven, E. M.: The small-for-date infant. II. Neurological and intellectual sequelae., Pediatrics **50:** 50, 1972.
23. Stuart, H. C.: Percentile chart for measurements of infant boys, Children's Medical Center, Boston, Mass.
24. Ounsted, M., and Sleigh, G.: The infant's self-regulation of food intake and weight gain, Lancet **2:** 1393, 1975.
25. McKeown, T., and Record, R. G.: Observations on foetal growth in multiple pregnancy in man, J. Endocrinol. **8:** 386, 1952.
26. Moustgaard, J.: Nutritive influences upon reproduction, J. Reprod. Med. **7:** 275, 1971, **8:** 1, 1972.
27. Winick, M.: Nutrition and the growing fetus, Ob./Gyn. pp. 47-49, 1972.
28. Widdowson, E. M.: Immediate and long-term consequences of being large or small at birth: A comparative approach, *in* Size at Birth, Ciba Foundation Symposia, Amsterdam, 1974, Associated Scientific Publishers, pp. 65-82.

Combined outpatient laparoscopic sterilization with therapeutic abortion

C. EDWIN POWE, JR., M.D.
JOHN A. McGEE, JR., M.D.
Charlotte, North Carolina

Combined outpatient laparoscopic sterilization and therapeutic abortion were evaluated at Charlotte Memorial Hospital and Presbyterian Hospital. Two hundred and four patients underwent the procedure, which proved to be safe and effective, requiring only a brief hospital stay. (AM. J. OBSTET. GYNECOL. 126: 565, 1976.)

THIS REPORT was prepared to evaluate the safety of performing the combined procedures using the outpatient setting. Other investigators[1-3] have studied the combination approach when performed on inpatients. From January 1, 1973, through December 31, 1975, at Charlotte Memorial Hospital and Presbyterian Hospital, 204 outpatients underwent therapeutic abortion and sterilization by suction evacuation of the uterus and laparoscopic tubal coagulation. There was little difference at the two institutions in anesthetic and surgical techniques. The procedures were performed by private gynecologists and gynecology residents. Age, parity, gestational age, surgical time, hospital stay, and complications were reviewed using hospital records. Follow-up evaluation was achieved by interviewing each primary-care physician and reviewing postoperative clinic records.

Material and methods

During the 3 years of this study, there were 204 cases of combined therapeutic abortion and laparoscopic tubal coagulation in patients under 13 weeks' gestation, with the mean gestational age being 9.4 weeks. The average patient age was 30.7 years of age, with 51 per cent of the patients falling into the 30 to 39 year age group. The average number of living children was 2.6, with eight patients having no children and 19 having five or more.

From the Department of Obstetrics and Gynecology, Charlotte Memorial and Presbyterian Hospitals.

Presented as official guest at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. C. Edwin Powe, Jr., 3535 Randolph Rd., Charlotte, North Carolina 28211.

The day prior to surgery a history, physical examination, complete blood count (CBC), urinalysis, Venereal Disease Research Laboratory (VDRL), blood type, and Rh factor were obtained. When indicated, chest x-ray, serum electrolytes, and electrocardiogram were performed. Patients were instructed not to eat or drink after midnight, and to report to the outpatient receiving area 1 hour prior to surgery. Abdominal or perineal shaving was not performed. The majority (58 per cent) were not given preoperative medication, but 42 per cent of the patients received 0.4 mg. of atropine and 50 mg. of meperidine intramuscularly.

Anesthesia varied somewhat at the two hospitals with 91 (45 per cent) patients receiving general endotracheal anesthesia, whereas 113 (55 per cent) patients were not intubated. Each group received thiopental, anectine, nitrous oxide, and fentanyl. Patients who had increased medical risk were not included in this study, since they were handled as inpatients. Previous surgery was not necessarily a contraindication to this surgery, with 13 per cent of the patients having had previous abdominal operations. Single-incision technique, using the Palmer-Jacobs operating laparoscope, was used in 44 per cent of the cases and a double-puncture method was used in 56 per cent of the cases. Following anesthesia, patients were placed in a modified lithotomy position. The abdomen, perineum, and vagina were scrubbed with Betadine, and the entire area was draped only once for both procedures. Dilatation of the cervix with either Pratt or Hegar dilators was followed by uterine evacuation with an 8 to 12 mm. vacuum cannula. Intravenous oxytocics were routinely used during evacuation. Following aspiration, either a vacuum cannula or a dilator was taped in place with a tenaculum on the cervix to allow for uterine positioning during tubal coagulation. After establishment of

Table I. Complications in outpatient sterilization with abortion (204 cases)

Complication	*No.*	*Per cent*
Uterine perforation; hysterectomy	1	0.5
Uterine perforation	2	1.0
Abortion hemorrhage	2	1.0
Total	5	2.5

Table II. Overnight observation in outpatient sterilization with abortion (204 cases)

Indication	*No.*	*Per cent*
Patient convenience	7	3.4
Abortion bleeding	2	1.0
Uterine perforation	1	0.5
Suspected respiratory aspiration	1	0.5
Total	11	5.4

pneumoperitoneum with 2 to 3 L of carbon dioxide; each oviduct was coagulated. Minor modifications of technique were utilized by individual operaters. In the majority of cases, the tubes were coagulated until visibly divided and no specimen was obtained.[6] Postoperatively patients were taken first to the recovery room, then to the observation area, from which they were discharged by a physician.

Results

The mean surgical time from incision to end of anesthesia was 38 minutes, with the mean hospitalization time from beginning of anesthesia to discharge from the outpatient department being 5 hours and 20 minutes. There was no difference in complications with the single or double-puncture techniques, nor with the endotracheal or nonendotracheal anesthesia. Thirteen patients (6.3 per cent) received antiemetics for nausea and vomiting, and 15 patients (7.4 per cent) received oral medication for abdominal or shoulder pain.

All complications are listed in Table I. The only major complication occurred from uterine perforation during suction curettage. Hemorrhage from the right uterine artery required abdominal hysterectomy for control of bleeding. The patient received 2 units of whole blood and was discharged in 7 days. No treatment was necessary for the remaining four patients. One pregnancy occurred following sterilization. There were no skin or bowel burns, bowel perforations, infections, or delayed complications.

The over-all complication rate was 2.5 per cent when both major and minor complications were included. Follow-up of 99 per cent was achieved in the 113 private patients and 77 per cent in the 91 staff patients.

Overnight observation was required for 11 cases (5.3 per cent) (Table II). Seven of these patients were observed for patient convenience, anxiety, or abdominal discomfort. Four were observed overnight for potentially serious complications which did not materialize.

Comment

The role of the surgical outpatient service has become increasingly important in the administration of health care. A complication rate in outpatients of 2.5 per cent in this series compares favorably with other reports[1, 2, 4] on inpatients undergoing the combined procedures. A recent study by Fishburne and associates[5] of combined first-trimester therapeutic termination with laparoscopic tubal sterilization on 108 outpatients echoes the experience reported here in terms of operating time, low number of complications, and a hospital stay averaging 5 hours.

When general anesthesia is utilized for laparoscopic surgery, endotracheal intubation has been recommended by a number of reports.[7–9] Anesthesia for the patients reported in this study was determined by the anesthesiologists in each of the two institutions that were studied. In order to achieve optimal conditions, endotracheal intubation was carried out for patients whenever an anesthetic or surgical difficulty was contemplated.

Samuels[10] studied 1,359 outpatient laparoscopic sterilizations performed at Presbyterian Hospital. In his series, 8 per cent were admitted for observation and therapy, whereas 5.3 per cent of the patients reported in this series undergoing combined procedures were admitted for observation. Complication rates for the two groups were 2 per cent for sterilization alone and 2.5 per cent for combined procedures. In this report, the major complications, which consisted of uterine perforation and uterine hemorrhage, were related to the pregnancy termination aspect of the combined procedures. The one pregnancy that followed tubal fulguration probably resulted from tubal nondivision or fistula formation.

Conclusion

In an outpatient setting at Charlotte Memorial Hospital and Presbyterian Hospital combined first-trimester termination with laparoscopic tubal sterilization proved to be a safe and effective procedure, requiring only a brief hospital stay.

REFERENCES

1. Whitson, L. G., Ballard, C. A., and Israel, R.: Obstet. Gynecol. **41:** 677, 1973.
2. Amin, H. K., and Neuwirth, R. S.: Fertil. Steril. **24:** 592, 1973.
3. Cunanan, R. G., and Courey, N. G.: J. Reprod. Med. **13:** 204, 1974.
4. Steptoe, P. C., and Imran, M.: Br. Med. J. **3:** 751, 1969.
5. Fishburne, J. I., Edelman, D. A., Hulka, J. F., and Mercer, J. P.: Obstet. Gynecol. **45:** 665, 1975.
6. Phillips, J., Keith, D., et al.: Gynecologic laparoscopy in 1975, J. Reprod. Med. 1976 (to be published).
7. Neuwirth, R. S.: Excerpta Medica, Amsterdam, 1971.
8. Cohen, M. R., Marshall, B. T., and Martin, B. E. K.: AM. J. OBSTET. GYNECOL. **108:** 458, 1970.
9. Hulka, J. F., Soderstrom, R. M., Corson, St., et al.: Complications Committee of the American Association of Gynecologic Laparoscopists first annual report. J. Reprod. Med. **10:** 301, 1973.
10. Samuels, W. R.: Personal communication: Outpatient sterilization by laparoscopy, presented October 1, 1974, to the North Carolina Obstetric and Gynecologic Society, Sea Island, Georgia.

Discussion

DR. JACK P. MERCER, Chapel Hill, North Carolina (by invitation). Drs. Powe and McGee have added further evidence of the safety of combined outpatient laparoscopic sterilization with therapeutic abortion. It is especially gratifying that their report confirms and closely parallels our previously reported[1] study in Chapel Hill. I find it interesting that this outpatient combined procedure has proved as successful in private practice as it has in a medical school environment.

In updating our previous experience, some new trends are evident. The previous study included 108 cases of combined outpatient laparoscopic sterilization with therapeutic abortion performed in North Carolina Memorial Hospital from September, 1971, to April, 1974. Seventy-seven additional cases have been added from April, 1974, through December, 1975.

In contrast to the Charlotte study, where all patients were given general anesthesia, 39 per cent of our 185 patients chose local anesthesia, increasing from 32 per cent in the earlier series to 47 per cent of the patients operated on in 1974 to 1975. Hulka and associates[2] clips were used to occlude the tubes in 33 per cent of our total cases, increasing from 29 per cent in the earlier group to 37 per cent of the cases in 1974 to 1975. General anesthesia was given for 91 per cent of our cautery patients, whereas local anesthesia was used for all but one patient in whom clips were applied.

We have also noted a rather striking change in the past 2 years in the length of time the patients stay in the hospital. While the mean operating time has remained virtually the same (30 minutes vs. 29 minutes), the total mean hospitalization time has decreased from 5 hours and 7 minutes to 3 hours and 10 minutes. In case you believe this is due only to the increased use of local anesthesia, let me hasten to add that in the past 2 years the patients receiving a general anesthetic remained in the hospital an average of only 26 minutes longer (3 hours and 23 minutes vs. 2 hours and 57 minutes) than the patients receiving local anesthesia. I would anticipate that a similar reduction in hospitalization time will be noted in Charlotte and elsewhere as outpatient teams become more experienced in patient education, scheduling, and postoperative recovery. The enthusiasm of the personnel involved in our outpatient program has not only made the procedure more efficient but also has made it more pleasant for the patient, her family, and her doctor.

The authors have reported three uterine perforations, explaining that one of these occurred during the D & E. I would like to ask whether the other two perforations occured during the D & E or during the manipulation of the dilator used to position the uterus for the tubal cauterization. As we previously reported,[1] the use of a controlling uterine forceps[3] instead of a dilator for laparoscopic sterilization after abortion has been very satisfactory, with no perforations resulting from its use. The instrument is blunt and angled enough to safely position the recently evacuated uterus.

I have three final questions: (1) the authors state, "the one pregnancy that followed tubal fulguration probably resulted from tubal nondivision or fistula formation." If it was not investigated further, how do you know the round ligament was not fulgurated? (2) What contraceptive program was then provided for this patient? (3) Were routine Pap smears taken preoperatively and, if not, why?

REFERENCES

1. Fishburne, J. I., Edelman, D. A., Hulka, J. F., and Mercer, J. P.: Outpatient laparoscopic sterilization with therapeutic abortion versus abortion alone, Obstet. Gynecol. **45:** 665, 1975.
2. Hulka, J. F., Fishburne, J. I., Mercer, J. P., and Omran, K. F.: Laparoscopic sterilization with a spring loaded clip: A report of the first fifty cases, AM. J. OBSTET. GYNECOL. **116:** 715, 1973.
3. Hulka, J. F.: Controlling uterine forceps for laparoscopic sterilization after abortion: A new instrument, AM. J. OBSTET. GYNECOL. **116:** 884, 1973.

A new look at pelvic relaxation

A. CULLEN RICHARDSON, M.D.
JAMES B. LYON, M.D.
NANCY L. WILLIAMS, B.S., R.N.
Atlanta, Georgia

The concept is presented that most cystoceles and/or urethroceles result from insolated defects in the connective tissue supports of the anterior quadrant of the pelvis. Four areas in which defects have been found to occur are identified. Sixty patients are presented who were found to have isolated defects in the endopelvic fascia at the lateral sidewall of the pelvis with significant cystourethroceles and stress urinary incontinence. The surgical treatment consisted only of a direct approach to and closure of the isolated defect. The operative results at 3 to 48 months were excellent in 91.7 per cent, improved in 5 per cent, and failed in 3.3 per cent. Discussion is offered of the possibility of the study of the pelvic floor from the viewpoint of a mechanical engineer. (AM. J. OBSTET. GYNECOL. 126: 568, 1976.)

PELVIC relaxation associated with urethrocele and/or cystocele has been usually ascribed to a generalized relaxation or attenuation and stretching of the connective tissue supports of the anterior quadrant of the pelvis.[1-3] Several years ago the authors began to feel that generalized stretching or attenuation of the anterior quadrant fascia was the exception, if it occurred at all. With careful physical examination, isolated areas of weakness could be detected in either the pubocervical fascia or pubourethral ligaments of patients with cystocele and/or urethrocele. This suggested an isolated defect in one of these structures. The defects were found to occur in four different areas. It appeared that all patients with cystocele and/or urethrocele had one or more of the four defects. This observation led the authors to decide that most cystoceles and/or urethroceles were the result of isolated defects or breaks in the pelvic connective tissue supports.

The pubocervical fascia was described as the principal static support of the bladder and urethra by Curtis, Anson, and McKay[4] in 1939. They discussed the relationship of this supporting layer to cystocele and urethrocele. Krantz,[5] in 1951, called attention to the pubourethral ligaments which attach the distal urethra to the overlying symphysis.

The areas in the anterior quadrant of the pelvis in which defects were identified and the order of the frequency in which they were observed in this patient population was as follows.

1. Lateral defect. A defect is found in the fascia laterally at or near its attachment to the levator insertion in the lower margin of the superior pubic ramus. It usually results in a mild to moderate cystourethrocele, a loss of the urethrovesical angle, and significant stress urinary incontinence. It can be unilateral or bilateral.

2. Transverse defect. A transverse separation occurs in the pubocervical fascia from its insertion into the pericervical ring of connective tissue. It usually results in a large cystocele in which the bladder herniates beneath the mucosa of the anterior vaginal fornix. The urethra remains well supported with a good urethrovesical angle. There is rarely, if ever, stress urinary incontinence. If this defect is repaired improperly, however, the patient can develop severe stress incontinence postoperatively.

3. Midline defect. An anteroposterior separation of the fascia occurs between the vagina and overlying bladder and/or urethra. Depending on the length of the defect, it results in a cystocele and/or urethrocele. If the defect is beneath the vesical neck, there will be a loss of the urethrovesical angle and stress urinary incontinence. This defect is the one most easily repaired and excellent results can be expected with the Kelly-Kennedy type procedures.

From the Department of Gynecology and Obstetrics, Emory University School of Medicine at Crawford W. Long Memorial Hospital.

Presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. A. Cullen Richardson, 710 Peachtree St., N.E., Atlanta, Georgia 30308.

4. *Pubourethral ligament defect.* The defect results from a loss of the integrity of the pubourethral ligaments. It is the least common of the four defects. Repair can be extremely difficult as the defect allows the urethra to telescope externally beneath the symphysis, above an essentially intact anterior vaginal wall. The outward protrusion straightens the urethrovesical angle with troublesome and persistant stress urinary incontinence.

The major clinical problem initially was identification of the lateral defect as distinct from the midline defect. To make this distinction, a tongue blade was placed along the vaginal axis in either side of the vagina. The tongue blades were brought up to the lower margin of the symphysis. If there was still a cystourethrocele when the patient strained, the defect was considered to be midline. If there was no bulge, the defect was considered to be lateral. If the lateral defect was unilateral, then support on that side alone obliterated the bulge when the patient strained. In addition, if the examiner palpated carefully through the anterior vaginal wall along the posterior surface of the symphysis and superior pubic ramus, the lateral weakness could be detected. This finding was subtle, but definite and recognizable.

A combination of two or more of the above defects within the anterior quadrant of the pelvis was rarely seen. A posterior pelvic quadrant defect (enterocele) and/or a central pelvic fascial defect with uterine prolapse were frequently associated with one of the anterior quadrant defects.

It was decided that a reasonably satisfactory validation of the localized nature of the defects would be the clinical results obtained if the surgical correction were limited to the area of the defect. With this concept in mind, the authors abandoned all general plication operative techniques and those procedures which created abnormal anatomy. An attempt was made in surgery to approach each defect directly and to close the defect with the restoration of normal anatomy. The most common anterior quadrant defect which had been demonstrated was the lateral one in which the fascia separated from its lateral attachment at the levator muscle insertion. The results of the surgical treatment in this group of patients are reported at this time.

Material

Between January, 1971, and October, 1975, the authors operated on 93 patients (all from their private practice) with symptomatic anterior quadrant pelvic relaxation. Of these, 62 were deemed to have lateral defects which resulted in a cystourethrocele with significant stress urinary incontinence. Due to extensive scarring from previous surgery, two patients were treated with other operative procedures and thus eliminated from the study group. Of the remaining 60 with lateral defects, 15 were felt to have bilateral and 45 unilateral defects. Of the 45 unilateral defects, five were on the left side and 40 were on the right side. Six of the 60 patients had had a previous anterior vaginal repair but they did not have extensive scarring.

Method

It was decided that all patients with lateral defects should be treated with some type of retropubic procedure. After a few minor variations during the early months of the study, the following procedure became the routine treatment for cystocele and/or urethrocele associated with a lateral defect. Through a Pfannensteil incision, the retroupubic space is entered in the midline and dissection is carried laterally on the affected side(s), separating the bladder entirely from the pubic ramus anteriorly and from the urethra and anterior one third of the vagina below. The dissection is carried cautiously downward until the upper 2 to 3 cm. of the medial attachment of the levator muscle come into view. At this time, defect in the lateral expanse of the pubocervical fascia is detectable. The medial margin of the separation has usually retracted almost to, if not to, the lateral superior sulcus of the vagina. With a finger in the vagina, the superior lateral sulcus of the vagina is elevated and sutures are placed through the fascia adjacent to the superior lateral vaginal sulcus and then into the semitendinous insertion of the levator muscle into the superior pubic ramus. Four to six such sutures are placed. Care is taken to avoid the numerous small veins in the area and also to avoid the periosteum of the pubic ramus. If hemostasis is satisfactory, no drains are inserted and the abdomen is closed. Because the procedure is carried out at a distance from the vesical neck, no appreciable edema or inflammatory reaction develops around the urethrovesical junction, and neither suprapubic nor transurethral drainage of the bladder is necessary.

Results

The follow-up in this group varies from 3 to 48 months, with an average of 20 months for all patients. Fifty-eight of the 60 patients have had satisfactory results. Of these, five state that they have stress urinary incontinence with coughing on rare occasions but not of such a degree to be considered by them a problem. Three, although greatly improved, still feel that their control is not quite as satisfactory as they would like it to be. There have been only two operative failures, and

both were apparent at 6 weeks after surgery. One was an error in the preoperative assessment of the patient, for she returned with a cystourethrocele (midline defect) in spite of good lateral support on each side. She was subsequently cured with a Kelly urethroplasty. The second failure was in a patient who had had a previous extensive repair. A Moskowitz procedure for an enterocele was done at the same time as the repair of the lateral pelvic wall defect. At 4 weeks after surgery, she felt "something pull" while coughing and both the enterocele and cystocele recurred. The follow-up of 3 to 48 months gives an over-all functional result of satisfactory to excellent in 91.7 per cent of the patients, improved in 5.0 per cent and failed in 3.3 per cent. This compares favorably with many published reports.[6–9] The anatomic results at this time are the same as the functional results.

An additional gratifying finding has been the shortened postoperative hospital stay. The postoperative stay averaged 4.9 days for all patients despite the fact that 45 patients (75 per cent) had additional major intra-abdominal procedures, such as hysterectomy and/or enterocele repair.

During the early part of the series, suprapubic cystotomy tubes were inserted in six cases. All of the suprapubic tubes were removed by the third day and none of these patients required catheterization. In the remaining 54 patients who did not have suprapubic drainage, only four (7 per cent) required catheterization. Three required catheterization one to three times. Only one patient required an indwelling catheter for 24 hours, and she had the only recorded urinary tract infection in the series. No serious complications occurred. There have been no instances of postoperative urgency incontinence or osteitis pubis.

Comment

The final evaluation of the results of this report requires additional follow-up. It is reassuring, however, that the two failures and three satisfactory, but not excellent results, were apparent immediately. There had been no change in the functional or anatomic results in any patient after 6 weeks postoperative evaluation. In the future it is possible that some patients will develop defects in other locations.

A preponderance of right lateral over left lateral defects was observed (40 on the right and five on the left). A possible explanation could be that the sigmoid colon and the mesosigmoid provide additional protection to the pelvic floor on the left.

Only six of the above 60 patients had had some type of previous anterior vaginal surgery. One of the failures was in this group. This operative approach may not be as useful if it is performed as a secondary procedure as compared with its effectiveness as a primary procedure. Once the anatomy has been distorted by an anterior vaginal plication, it is difficult to determine the location of the original primary defect. Furthermore, even if a lateral defect is evident, the previous plication may have so shortened the supports in the midline as to make it surgically impossible to close the defect laterally.

This report is intended to document the concept of localized defects in the pubocervical fascia as the cause of most anterior pelvic quadrant relaxation and to emphasize the importance of this concept in the selection of the primary operative procedure, which should be based on an assessment of the anatomic defect in each individual patient. The surgical procedure described above is easily performed and has served the authors well. The results obtained were very satisfactory. It is readily admitted, however, that there are other procedures that will accomplish the same desired result, which is the correction of the isolated defect.

As in the case of anterior quadrant defects, it is felt that relaxation in the posterior pelvic quadrant and in the central pelvis also frequently results from localized breaks in the continuity of the supporting structures. A specific surgical approach to these areas as well as the other anterior quadrant defects has likewise been practiced since January, 1971. These results will be the subject of a later report.

The nature and etiology of the localized defects of the endopelvic fascia remain undetermined. It seems likely that at least some of these defects are actual tears in the fascia. On gross examination at the time of surgery, the appearance of the defect is often exactly as one might expect of an actual tear. How and when such tears would occur is not as yet apparent. Occasionally, a patient can recall the exact time when she felt "something pull" during physical exertion. Subsequently, she noted soreness in her lower abdomen and a few weeks later began to experience pelvic pressure and stress urinary incontinence. Frequently, however, the onset was totally insidious.

A surgical repair of the pelvic floor is, in fact, an exercise in mechanical engineering. An engineer* is now participating with the authors in their continuing study of this problem. He has suggested that the pelvic floor should be approached as one might study the capacity of a suspension bridge. Such a viewpoint leads one to ask questions about (1) the structural compo-

*Hyland Y. L. Chen, Ph.D., Assistant Professor, School of Engineering Science and Mechanics, Georgia Institute of Technology, Atlanta, Georgia.

nents, (2) the architectural configuration, and (3) the potential loads to be applied.

As to the structural components, one would want answers to the following questions: What structures in the pelvis actually have the capacity to bear weight? What is the tensile strength of the tissue components of each structure? How do they behave under stress? What are the differences in the capacities of these structures to withstand dynamic or impact stress and static or chronic stress? How does this capacity change with age, nutrition, and/or hormonal status? How does the weight-bearing capacity of these structures correlate with the relative amount of collagen, elastin, smooth muscle, and ground substance when seen with light microscopy? Are there qualitative or chemical changes in one or more of these components?

Regarding its structural configuration, one would ask: What is the architecture and configuration of the supporting tissues? Is the contour of the pelvic floor such as to create high stress points, and does this change with parity, obestiy, or age? Is the distribution of supporting structures such that there are inherently weak and strong areas?

When considering the potential load to be applied the questions would be: What is the pressure applied to the pelvic floor, and what factors influence the variations in pressure? Is the load transmitted invariably as hydrostatic pressure, or is there a "ball-in-sling" effect? Does the pelvic floor sometimes give way purely as a result of "overloading"? If so, what can be done to decrease the load?

These and many other questions need to be answered before the best surgical treatment of pelvic relaxation can be determined and before intelligent consideration can be given to prevention of this problem.

REFERENCES

1. Danforth, D. N., editor: Textbook of Obstetrics and Gynecology, ed. 2, New York, 1966, Harper & Row, Inc., p. 828.
2. Brewer, J. I.: Textbook of Gynecology, ed. 3, Baltimore, 1961, The Williams & Wilkins Company, pp. 121 and 404.
3. Jeffcoate, T. N. A.: Principles of Gynecology, ed. 2, Washington, 1962, Butterworth & Company, Ltd., p. 725.
4. Curtis, A. H., Anson, B. I., and McKay, C. B.: Surg. Gynecol. Obstet. **68:** 161, 1939.
5. Krantz, K. E.: Am. J. Obstet. Gynecol. **62:** 374, 1951.
6. Haydon, G. B., and Yonkilis, M. H.: Obstet. Gynecol. **35:** 898, 1970.
7. Ball, T. J., Knapp, R. C., Nathanson, B., and Lagasse, L. D.: Am. J. Obstet. Gynecol. **94:** 997, 1966.
8. Burch, J. C.: Am. J. Obstet. Gynecol. **100:** 764, 1968.
9. Green, T. H.: *In* Reid, D. E., and Christian, C. D., editors: Controversy in Obstetrics and Gynecology II, Philadelphia, 1974, W. B. Saunders Company, p. 395.

Discussion

Dr. Mark Pentecost, Jr., Atlanta, Georgia (Official guest). Dr. Richardson has presented an intriguing and interesting preliminary report on anterior quadrant pelvic relaxation with many new ideas. The authors' goal has been to search out and identify specific anatomic defects in pelvic relaxation producing stress urinary incontinence and to perform a procedure to repair the specific anatomic defect and thereby restore normal anatomy, which is in contrast to the general plication procedures.

The underlying premise is that there must be a specific defect or tear as opposed to a genearlized defect such as stretching or attenuation of fascia and ligaments. The report of Francis[1] that stress urinary incontinence develops during pregnancy rather than at the time of delivery and improve post partum would suggest that attenuation and stretching do play a role in pelvic relaxation.

From their findings the authors have identified four areas in which defects have been found to occur and have arranged them in order of their frequency. Surprisingly, the most common is the lateral defect. I would have thought the midline defect more common, as the Kelly type midline plication produces good results in a large percentage of cases.[2] If this finding is substantiated, it is very important. If the defect is lateral to where we are repairing, we have only taken a tuck and not really corrected the situation and would expect this to gradually fail. We are in a sense splicing the rope at the wrong place.

Since so much of the investigation of pelvic relaxation with stress urinary incontinence has used the urethrocystogram, it would seem very helpful to obtain this type of study both preoperatively and postoperatively to compare and correlate this study with other work. One might speculate that the authors' midline defect might produce the Type I incontinence described by Green[3] and that the lateral defect might be one source of Green's Type II incontinence. Another source of Type II incontinence might be the pubourethral ligament defect described. If this speculation is correct, then the authors' double tongue blade urethrovesicle elevation test would be a simple, inexpensive clinical method ot help in deciding on the type of corrective procedure to use. Also the authors make a strong point of restoring normal anatomy. These x-ray studies would be helpful in proving or disproving this point. I ask the question: does the authors' unilateral procedure pull the urethra to that side?

The authors do not seem to be stressing their opera-

tive procedure as much as their concepts, but perhaps they should. The results do compare favorably with many published reports and the postoperative course is remarkable in that there is a very low incidence of voiding problems, bladder drainage, and urinary tract infection. In addition, the hospital stay is shortened and the authors describe the procedure as being easily performed.

Finally, the authors' report is intended to document the concept of localized defects in the pubocervical fascia as the cause of most anterior quadrant pelvic relaxation. The fact that they have identified 45 unilateral defects out of 60 cases and performed a unilateral repair with excellent results would appear to offer strong support. Studying the authors' description of their procedure and assuming the role of the devil's advocate, I speculate that in using four to six sutures in the repair they are performing such a superb suspension of the urethra and vesical neck that they are obtaining excellent results with a unilateral repair. In using four to six sutures, even if there is a tear or defect, one questions if there is a degree of general plication.

In conclusion, I would like to compliment Dr. Richardson and his co-authors on this preliminary report. Dr. Richardson produces great admiration and some envy that a busy clinician is combining a wealth of clinical experience with basic investigation to rethink this complicated and still unsolved problem of pelvic support and relaxation.

REFERENCES

1. Francis, W. J. A.: The onset of stress incontinence, J. Obstet. Gynaecol. Br. Emp. **67:** 899, 1960.
2. Te Linde, R. W., and Mattingly, R. F.: Operative Gynecology, ed. 4, Philadelphia, 1970, J. B. Lippincott Company, p. 547.
3. Green, T. H., Jr.: Development of a plan for the diagnosis and treatment of urinary stress incontinence, AM. J. OBSTET. GYNECOL. **83:** 632, 1962.

DR. PAUL W. TAYLOR, JR., Vero Beach, Florida (Official guest). Dr. Richardson's paper appeals to my basically simple nature and my desire to simplify complicated problems like stress incontinence. Find a fascial defect in the anterior quadrant of the pelvis that causes cystocele, urethrocele with stress incontinence, then surgically correct it with six to eight sutures to attain normal anatomy and a cure. By doing this, hospital stay is cut down by serveral days, major complications are eliminated—including urinary tract infections, the bane of pelvic surgeons—and good results are attained. It almost sounds too simple.

The literature on stress incontinence is anything but simple. There are multiple operations for correction of stress urinary incontinence which probably indicates ultimate inadequacies in all. Perhaps this is why Dr. Richardson and his group have tried to "build a better mousetrap" with their procedure in this paper.

Stress urinary incontinence has been categorized by the experts into Type I (loss of posterior urethrovesical angle) and Type II (loss of posterior urethrovesical angle and downward and backward rotation of the urethral axis). Simplified, Type I is correctible surgically with a Kelly type plication and Type II with a vaginal plication and a suprapubic suspension such as the Marshall-Marchetti-Krantz procedure.

Dr. Richardson's midline defects in his 60 patients were few in number but, as suspected, these defects were adequately corrected by Kelly type vaginal plication as in a Type I stress urinary incontinence.

The pubourethral ligamentous defects would correspond to a Type II defect. These were few in numbers. Were these defects treated by repair of fascial defects and/or a Marshall-Marchetti-Krantz procedure?

The transverse defects are no problem as they exist as far as stress urinary incontinence, but overcorrection by either repair of fascial defect or purse-string plication might cause stress incontinence. How were these handled?

The lateral defects, 45 of them, somewhat perplex me (most of the defects being in the midline appeals to me). Are there physiologic x-ray studies using either cinefluoroscopy or the chain cystourethrogram to show before and after films showing the type of stress urinary incontinence and what changes are wrought by repair?

I like the simple tongue blade test. It is straightforward, like the Marchetti-Read-Bonney test that we have used with the ovum forceps to re-establish on examination the posterior urethrovesical angle. Did two examiners agree of the four types of defects? Since this might be an arbitrary thing, I think it is important in a new concept. Were 60 asymptomatic control subjects studied for fascial defects? This might be interesting. What type of suture was used?

Why were the fascial defects on the right side in 40 out of 45 patients? Perhaps the increased strain of dextrorotation of the uterus during pregnancy with no sigmoid colon or mesosigmoid for buffer as the left side has explains it.

Dr. Richardson seems to dismiss attenuation and stretching of pelvic supporting structures, but I think they do occur. Pregnancy with onset of stress incontinence—cured by delivery—displays this. Fascial tears can best explain rapid formation of cystocele and urethrocele with stress incontinence in asymptomatic patients after heavy lifting and straining, penumonia with coughing, and so on.

REFERENCES

1. Green, T. H.: *In* Reid, D. E., and Christian, C. D., editors: Controversy in Obstetrics and Gynecology II, Philadelphia, 1974, W. B. Saunders Company, p. 395.
2. Durfee, R. B.: *In* Reid, D. E., and Christian, C. D., editors: Controversy in Obstetrics and Gynecology II, Philadelphia, 1974, W. B. Saunders Company, p. 385.
3. Hodgkinson, C. P.: *In* Reid, D. E., and Christian, C. D.,

editors: Controversy in Obstetrics and Gynecology II, Philadelphia, 1974, W. B. Saunders Company, p. 412.
4. Grant, J. C. B.: A Method of Anatomy, ed. 4, Baltimore, 1966, The Williams & Williams Company, p. 307.
5. Rob, C., and Smith, R.: Gynecology and Obstetrics, Philadelphia, 1971, J. B. Lippincott Company, p. 117.
6. Novak, E., K. Jones, G. S., and Jones, H. W., Jr., editors: Novak's Textbook of Gynecology, ed. 8, Baltimore, 1970, The Williams & Wilkins Company, p. 257.
7. Te Linde, R. W.: Operative Gynecology, ed. 3, Philadelphia, 1962, J. B. Lippincott Company, p. 177.
8. Cunningham, D. J.: *In* Brash, J. C., editor: Cunningham's Textbook of Anatomy, ed. 9, London, 1951, Oxford University Press, p. 465.
9. Greenhill, J. P., editor: The Yearbook of Obstetrics and Gynecology 1975, Chicago, 1975, Year Book Medical Publishers, Inc., p. 324.
10. Parsons, L., and Sommers, S. C.: Gynecology, Philadelphia, 1964, W. B. Saunders Company, p. 1034.

Corynebacterium vaginale (Haemophilus vaginalis) in women with leukorrhea

WILLIAM E. JOSEY, M.D.
WILLIAM J. McKENZIE, M.D.
DWIGHT W. LAMBE, JR., PH.D.
Atlanta, Georgia

Corynebacterium vaginale *was recovered from vaginal-cervical swab specimens in 164 of 288 women with leukorrhea and in four of 30 women without signs or symptoms of lower genital tract infection. The amount and character of the leukorrhea observed in association with* C. vaginale *infection were variable; in typical cases the discharge had the appearance of a thin paste. In a series of 100 patients studied to determine the apparent causes of leukorrhea, noninfectious causes were inferred in seven patients and no cause ascertained in six. Candida or other yeasts,* C. vaginale, *and* Trichomonas vaginalis *were identified alone or in combination in 87 patients; 53 had yeasts, 35 had* C. vaginale, *and 15 had* T. vaginalis. (AM. J. OBSTET. GYNECOL. 126: 574, 1976.)

CORYNEBACTERIUM VAGINALE has been widely described as one of the causes of infectious leukorrhea.[1-6] However, not all investigators have confirmed a pathogenic role for this agent.[7-9] The present investigation was undertaken to reevaluate the relation of *C. vaginale* to leukorrhea, using methods of isolation and identification similar to those recently developed by Dunkelberg, Skaggs, and Kellogg,[10] for greater precision in laboratory diagnosis.

Materials and methods

Study groups. All of the women included in this investigation were private patients attending the Emory University Clinic. Vaginal-cervical specimens for culture were obtained in 288 patients found to have leukorrhea on examination. Wet mount preparations were also made in the majority of these patients. The age range of the women in this group was 14 to 69 years, and all were sexually active.

Cultures were also obtained in 30 sexually active women with no signs or symptoms of lower genital tract infection. The age range of this group was 19 to 47 years.

In order to determine the relative frequency of this infection as compared to the frequency of trichomoniasis and candidiasis in patients with leukorrhea, a series of 100 patients presenting with leukorrhea were studied exclusively by one of us (W. E. J.) Wet mount preparations were made in all of the 100 patients to look for trichomonads, Candida filaments, and *C. vaginale* "clue cells." Also included in this group were 60 patients in whom cultures were obtained as part of the diagnostic evaluation.

Culture methods. Vaginal-cervical swab specimens were placed in a sterile culture tube and taken immediately to the laboratory, where the swabs were streaked on peptone-starch-dextrose agar (PSD), chocolate agar, sheep blood agar, MacConkey's agar (Difco), and Thayer-Martin medium. The blood agar and MacConkey's agar plates were incubated at 37° C. aerobically; the PSD agar, chocolate agar, and Thayer-Martin plates were incubated in a candle jar to provide the increased CO_2 tension needed for optimum growth of *C. vaginale* and *N. gonorrhoeae*. No attempt was made in this investigation to isolate obligate anaerobes.

From the Department of Gynecology and Obstetrics and the Department of Pathology, The Woodruff Medical Center of Emory University and Emory University School of Medicine.

Supported in part by the Teaching and Research Fund of the Emory University Clinic.

Presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: William E. Josey, M.D., Emory University Clinic, 1365 Clifton Rd. N.E., Atlanta, Georgia 30322.

In accordance with the recommendation of Dunkelberg, Skaggs, and Kellogg,[10] suspected *C. vaginale* colonies were selected from the PSD agar plates with a dissecting microscope with ×40 magnification. Suspected colonies were also selected from the chocolate agar plates if typical colonies were absent on the PSD agar plate. The biochemical tests that were used for specific identification of *C. vaginale* have been described elsewhere.[11]

Results

Of the 288 women with leukorrhea, 164 had positive cultures for *C. vaginale.* In six others, organisms were recovered that did not fulfill all of the biochemical criteria for positive identification; these organisms were reported as "Corynebacterium species."

In the group of 30 women without any symptoms or signs of lower genital tract infection, four had positive cultures for *C. vaginale.*

One or more other lower genital tract infections were diagnosed concomitantly in 59 women harboring *C. vaginale.* There were 22 cases of yeast infection, 21 of trichomoniasis, 12 of condyloma acuminatum, seven of genital herpes, and six of gonorrhea.

Almost all other organisms isolated from the vagina and cervix were those generally acknowledged to be normal constituents of the vaginal flora. Large numbers of these organisms, including lactobacilli, diphtheroids, streptococci, staphylococci, enterococci, and gram-negative rods such as *E. coli,* were isolated in both *C. vaginale*–positive and *C. vaginale*–negative patients. There was no indication that any of these organisms were causally related to the observed discharges, with the possible exception of two *C. vaginale*–negative cases in which the cultures were overgrown with *Proteus mirabilis;* in both cases the patients had received intensive antibiotic therapy, and the relation of the Proteus infection to the observed leukorrhea is problematic.

The signs and symptoms associated with *C. vaginale* infection were evaluated primarily in those patients in whom no other specific infection was evident. The amount of associated discharge ranged from slight to copious. The character of the discharge was also variable. The type of discharge observed most frequently had the appearance of a thin paste and tended to adhere to the vaginal wall. In some cases, a milky discharge was noted to flow onto the vulva. Gross inflammation of the vagina was rarely observed. A distinctive odor could be detected in many patients during speculum examination. Few symptoms other than vaginal discharge were reported by patients harboring *C. vaginale.* About one fifth volunteered the complaint of a vaginal odor, and some others admitted the presence of an odor when questioned about this symptom. A vague irritation was experienced by some patients, but itching was unusual in the absence of associated yeast infection.

Table I. Apparent causes of leukorrhea in 87 patients

	Number
Candida or other yeasts	44
C. vaginale	22
Trichomonas vaginalis	7
Candida + *C. vaginale*	6
T. vaginalis + *C. vaginale*	5
Candida + *T. vaginalis* + *C. vaginale*	2
Candida + *T. vaginalis*	1

In the series of 100 patients studied to determine the apparent causes of leukorrhea, noninfectious causes were inferred in seven patients (chronic cervicitis in three, atrophic vaginitis in two, possible desquamative vaginitis in one, and intrauterine device reaction in one). In six patients no cause was ascertained. Among the other 87 patients, vaginal yeast infection was diagnosed by wet mounts and/or cultures in 53, and trichomonal infection was diagnosed by wet mounts in 15. *C. vaginale* infection was diagnosed by culture in 33 patients. This diagnosis was also suggested by the findings in wet mount preparations in two other patients in whom cultures were not obtained. The numbers of patients in whom each agent or combination of agents were identified are shown in Table I.

Comment

Corynebacterium vaginale, otherwise known as *Haemophilus vaginalis,* is a small, pleomorphic, gram-variable but predominantly gram-negative, nonmotile rod. Like *Neisseria gonorrhoeae, C. vaginale* is a fastidious organism, growing best in a reduced oxygen atmosphere. Currently recommended standards for its laboratory recognition were established by Dunkelberg, Skaggs, and Kellogg[10] at the U. S. Public Health Service Center for Disease Control. To date, its proper classification remains unsettled, since it does not clearly fit into either the genus Haemophilus or the genus Corynebacterium.

Despite a considerable volume of literature on the subject, there is still some controversy as to whether *C. vaginale* is a true vaginal pathogen or a normal constituent of the vaginal flora. Although the majority of studies have tended to substantiate the thesis of Gardner and Dukes[1] that this agent is the cause of most vaginitides formerly called "nonspecific," many of the earlier studies may be criticized on account of the

employment of questionable criteria for its identification.

Even with the use of more precise laboratory methods, the pathogenicity of *C. vaginale* is hard to assess. Gardner and Kaufman[6] described it as a strictly surface parasite that alters the consistency of the vaginal secretions and slightly elevates the vaginal pH without invading the tissues. Although its occasional appearance in the blood stream in association with obstetric and neonatal sepsis has been reported,[12] the significance of these observations remains to be determined.

In addition to its weak or absent invasive power, the frequent association of *C. vaginale* with other agents presents another problem complicating the assessment of its relationship to leukorrhea. Several studies have documented the occurrence of *C. vaginale* in association with *Trichomonas vaginalis.*[11] In the present study, we diagnosed various concurrent lower genital tract infections, including yeast infection, trichomoniasis, condyloma acuminatum, genital herpes, and gonorrhea, in 59 or 36 per cent of 164 *C. vaginale*–infected women exhibiting leukorrhea.

The assessment of pathogenicity is rendered further difficult by the finding of *C. vaginale* in some women with no symptoms or signs of lower genital tract infection. Dunkelberg and associates[3] isolated *C. vaginale* in 10.7 per cent of 550 women with no evidence of vaginitis. Lewis and associates[4] isolated the agent in 9.5 per cent of 759 women without vaginitis. In the present study, we isolated *C. vaginale* in four (13 per cent) of 30 women without any symptoms or signs of lower genital tract infection. It should be emphasized, however, that the problem of asymptomatic or inapparent infection is well recognized for most other microbial agents known to infect the male and female genitourinary organs; hence, the occasional isolation of *C. vaginale* in the apparently healthy vagina does not controvert a pathogenic role for this agent.

Other than the human inoculation experiments conducted by Gardner and Kaufman,[6] the best evidence of pathogenicity has been the frequency with which *C. vaginale* is recovered from the vagina in women with leukorrhea, and the disappearance of the abnormal discharge when the organisms are eradicated from the vagina.[2] Gardner, Dampeer, and Dukes[13] identified *C. vaginale* in 46.5 per cent of 1,211 women with vaginitis, Dunkelberg and associates[3] identified it in 34 per cent of 431 with vaginitis, Lewis and associates[4] identified it in 47 per cent of 249 with vaginitis, and Akerlund and Mardh[5] identified it in 31.4 per cent of 70 with vaginitis. The comparable figures in the present study were 164 of 288, or 57 per cent.

The most characteristic sign associated with *C. vaginale* infection seems to be a pasty discharge that clings to the vaginal wall. However, the amount and character of the leukorrhea vary considerably. A distinctive odor may be present, and is the only frequently voiced symptom other than the annoying discharge.

In the series of 100 patients studied to determine the apparent causes of leukorrhea, *C. vaginale* was identified alone in 22 patients, in association with Candida in six, in association with *Trichomonas vaginalis* in five, and with both Candida and *T. vaginalis* in two. As an apparent cause of leukorrhea, *C. vaginale* infection was intermediate in frequency between yeast infection and trichomoniasis.

Available epidemiologic data strongly suggest that *C. vaginale* is transmitted sexually. Thus, in studies of the husbands of women infected with *C. vaginale,* Gardner and Kaufman[6] demonstrated urethral colonization in 91 of 101 men examined. In addition to the association of *C. vaginale* infection with various sexually transmitted diseases, we have noted a high rate of marital instability among infected women, and have documented an increased frequency of cervical neoplasia as has previously been found for certain other sexually transmitted diseases, including trichomoniasis and genital herpes.[11]

Although Gardner and Kaufman[6] emphasized the diagnostic value of the "clue cell" (an epithelial cell with a stippled appearance due to adherence of the organisms on its surface), we agree with Akerlund and Mardh[5] that this finding in wet mount preparations is not entirely specific. The usefulness of the wet smear is also hampered by the frequent occurrence of *C. vaginale* vaginitis in association with trichomoniasis and candidiasis. In our opinion, diagnostic accuracy is not possible without the use of appropriate culture methods.

To maintain viability of the organisms in transit, Dunkelberg, Skaggs, and Kellogg recommended Proteose Peptone No. 3 (Difco). Akerlund and Mardh[5] have found a modified Stuart's medium to be a satisfactory transport medium for *C. vaginale* as well as *N. gonorrhoeae.* Currently, we are also using a modified Stuart's medium (Amies') medium to transport vaginal-cervical swab specimens to the laboratory for culturing both of these agents.

A variety of local and systemic antibacterial agents have been recommended for the treatment of *C. vaginale* infection. Our experience supports the reported efficacy of both ampicillin[12, 14] and cephalexin,[12] although seemingly resistant strains of *C. vaginale* have been encountered. We consider it futile to treat the sexually active woman without simultaneously treating her husband or sexual partner.

REFERENCES

1. Gardner, H. L., and Dukes, C. D.: *Haemophilus vaginalis* vaginitis, AM. J. OBSTET. GYNECOL. **69:** 962, 1955.
2. Brewer, J. I., Halpern, B., and Thomas, G.: *Haemophilus vaginalis* vaginitis, AM. J. OBSTET. GYNECOL. **74:** 834, 1957.
3. Dunkelberg, W. E., Jr., Hefner, J. D., Patow, W. E., Wyman, F. J., Jr., and Orup, H. I.: *Hemophilus vaginalis* among asymptomatic women, Obstet. Gynecol. **20:** 629, 1962.
4. Lewis, J. F., O'Brien, S. M., Ural, U. M., and Burke, T.: *Corynebacterium vaginale* vaginitis, AM. J. OBSTET. GYNECOL. **112:** 87, 1972.
5. Akerlund, M., and Mardh, P. A.: Isolation and identification of *Corynebacterium vaginale (Haemophilus vaginalis)* in women with infections of the lower genital tract, Acta Obstet. Gynecol. Scand. **53:** 85, 1974.
6. Gardner, H. L., and Kaufman, R. H.: Benign diseases of the vulva, St. Louis, 1969, The C. V. Mosby Company, pp. 191-207.
7. Heltai, A., and Taleghany, P.: Nonspecific vaginal infections. A critical evaluation of *Haemophilus vaginalis,* AM. J. OBSTET. GYNECOL. **77:** 144, 1959.
8. Frampton, J., and Lee, Y.: Is *Haemophilus vaginalis* a pathogen in the female genital tract? J. Obstet. Gynecol. Br. Commonw. **71:** 436, 1964.
9. Robinson, S. C., and Mirchandani, G.: Observations on vaginal trichomoniasis. IV. Significance of vaginal flora under various conditions, AM. J. OBSTET. GYNECOL. **91:** 1005, 1965.
10. Dunkelberg, W. E., Jr., Skaggs, R., and Kellogg, D. S., Jr.: Method for isolation and identification of *Corynebacterium vaginale (Haemophilus vaginalis),* Appl. Microbiol. **19:** 47, 1970.
11. Josey, W. E., and Lambe, D. W., Jr.: Epidemiologic characteristics of women infected with *Corynebacterium vaginale (Haemophilus vaginalis),* J. Am. Vener. Dis. Assoc. In press.
12. Monif, G. R. G.: Infectious diseases in obstetrics and gynecology, Hagerstown, Md., 1974, Harper & Row, Publishers, Inc., pp. 127-130.
13. Gardner, H. L., Dampeer, T. K., and Dukes, C. D.: The prevalence of vaginitis, AM. J. OBSTET. GYNECOL. **72:** 1080, 1957.
14. Lee, L., and Schmale, J. D.: Ampicillin therapy for *Corynebacterium vaginale (Haemophilus vaginalis)* vaginitis, AM. J. OBSTET. GYNECOL. **115:** 786, 1973.

Discussion

DR. HARRY. W. JARRETT, Lynchburg, Virginia (official guest). Dr. Josey has further demonstrated the pathogenicity of *Corynebacterium vaginale* as an etiologic agent in infectious leukorrhea of females. He confirms—what was first emphasized by Gardner and Dukes in 1955—that *Corynebacterium vaginale (Haemophilus vaginalis)* should be sought as a possible single cause of vaginitis or in association with trichomoniasis and/or candidiasis.

Dr. Josey confirms what others have stated: that physicians can make precise diagnoses of vaginitis using clinical judgment, wet smears, and cultures. He does not mention the additional use of Pap smears in the diagnosis of vaginitis as investigated and reported by McLennan, Smith, and McLennan.[1] Burmeister and Gardner[2] have stated that 95 per cent of vaginitis is due to Trichomonas, *Haemophilus vaginalis,* or Candida. In contrast to Dr. Josey, they felt that these infections can be diagnosed readily by wet mount, and cultures are rarely necessary. They relied on making the diagnosis of *Corynebacterium vaginale* infection by correlating clinical and laboratory findings. The wet mount examination is said to show "clue cells," characteristically few pus cells, and no lactobacilli.

In the last several years, in my private practice, I have adopted an approach for diagnosing and treating the woman with vaginitis which has been satisfactory. A solution for use in preparing wet mounts was reported by Barchet.[3] I was unable to find locally the chemicals which he used and have been using Parker's Blue-Black Ink mixed with normal saline to identify pathogens. In addition to the wet mount, cultures for gonorrhea and candida are obtained by utilizing Transgrow and Nickerson's media. In those cases where the cause of the vaginitis is thought to be infectious in nature, no trichomonas is found on wet mount, both Transgrow and Nickerson media are negative, and the wet mount is diagnostic or suggestive, a diagnosis of Corynebacterium has been made. A culture for *Corynebacterium vaginale* has not been obtained except in persistent cases of vaginitis. These cultures are available locally but cost $10.00 and necessitate transportation to a laboratory. I have talked with our bacteriologist and he informs me that this organism is difficult to grow. I wonder if these cultures are a justifiable expense for our patients to be used as a routine procedure.

Dr. Josey has found that the three main causes of vaginitis—*Corynebacterium vaginale,* Candida, and Trichomonas—are singly and in combination responsible for 87 per cent of vaginitis in the patients seen exclusively by him. *C. vaginale* was found in 57 per cent of his large group and 35 per cent in a group of 100. I wonder if this does not represent a difference in socioeconomic groups as had been shown by others. Should we physicians consider this when diagnosing vaginitis?

I would like to have Dr. Josey's comments on the following questions: (1) Do you feel the Pap smear is of any value in determining the etiology of vaginitis? (2) Do you feel the plan I have outlined to determine the cause of vaginitis is acceptable for practitioners who do not have readily available laboratory facilities to handle vaginal cultures? (3) Do you have any comments in regard to the preparation of wet mounts? (4) You present your findings prior to treatment, but were any cultures obtained following treatment to see if the organism had indeed been eliminated from the vagina? Also, was there any correlation found between wet mount interpretation and what was later found on cultures? (5) Would it be reasonable for us to treat our

patients, thought to have vaginitis due to an infection, for Corynebacterium when Trichomonas, Candida, and Gonorrhea have been eliminated as possibilities?

Dr. Josey continues to add to our knowledge of infectious diseases in obstetrics and gynecology. He further supports that *Corynebacterium vaginale* is the bacteria responsible for "nonspecific vaginitis." We should seek this organism as the etiology of vaginitis and, when it is found or suspected, appropriate therapy should be instituted.

REFERENCES

1. McLennan, M. T., Smith, J. M., and McLennan, C. E.: Diagnosis of vaginal mycosis and trichomoniasis, Obstet. Gynecol. **40:** 321, 1972.
2. Burmeister, R. E., and Gardner, H. L.: Vaginitis diagnosis and treatment, Postgrad. Med. **48:** 159, 1970.
3. Barchet, S.: A new look at vaginal discharges, Obstet. Gynecol. **40:** 615, 1972.

YOU CAN EASE THE BURDEN OF CONSTIPATION OF PREGNANCY

effectively and gently

Suitable for general use in obstetrics[1]
Effective laxation was obtained in 324 (96%) of 336 pregnant women treated with SENOKOT laxatives, as reported in seven published studies,[2-8] with virtual freedom from side effects at proper dosage levels.

Gentle stimulation of peristalsis
Virtually colon-specific, SENOKOT Tablets/Granules provide overnight laxation through gentle neuroperistaltic stimulation of the motor plexus of Auerbach, not by irritation of bowel mucosa.
SENOKOT laxatives may be administered with milk and antacids.
Pregnant patients may be started on half the initial recommended dosage of SENOKOT Tablets/Granules, with gradual adjustment to the optimal maintenance dose for regular and comfortable evacuation.

References: **1.** Burgess, D. E.: Constipation in Obstetrics, in *Management of Constipation*, edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 179. **2.** Sarles, H., Camatte, R.: *Provence Med* 38:3 (Dec.) 1970. **3.** Scott, R. S.: *Western Med* 6:342 (Dec.) 1965. **4.** Blazy, G.: *Toulouse Med* 64:625 (June-July) 1963. **5.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **6.** Monias, M. B., *et al*: *Md State Med J* 9:439 (Aug.) 1960. **7.** Wager, H. P., Melosh, W. D.: *Quart Rev Surg Obst & Gynec* 15:30 (March) 1958. **8.** Herland, A. L., Lowenstein, A.: *Quart Rev Surg Obst & Gynec* 14:196 (Dec.) 1957.

Senokot laxative claims are documented

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8317 176176

SENOKOT® tablets granules

(standardized senna concentrate)

a natural vegetable laxative



TO RELIEVE POSTPARTUM CONSTIPATION EFFECTIVELY, YET GENTLY

choose a leading laxative in Ob/Gyn practice

Distinguished record of effectiveness

Clinical studies,[2-18] comprising 6,151 obstetric and gynecologic patients, showed that 5,874 or 95.5% responded to SENOKOT laxatives. In 5,527 postpartum patients given SENOKOT laxatives routinely, enemas were used in only 3.2%.

Gentle stimulation of peristalsis

SENOKOT Tablets/Granules are virtually colon-specific,[1] and provide gentle, predictable morning laxation when taken at bedtime. With flexible individualized dosage, you can provide welcome relief for the vast majority of your constipated postpartum patients.

References: 1. Godding, E. W.: Therapeutic Agents, in *Management of Constipation*, edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 65. **2.** Gonzales Genoves, M.: *Rev Bibliografia Med Internac* No. 329 (Nov.) 1968. **3.** Cuevas Leandro, M., Ramirez Varela, E.: *Semana Med de Mexico* 53: No. 742 (Sept. 27) 1968. **4.** Goya, P. A., Perez Vasquez, A.: *Rev Mexico Med* 3: No. 16, 1968. **5.** Monias, M. B.: *Md State Med J* 15:32 (Feb.) 1966. **6.** Scott, R. S.: *Western Med* 6:342 (Dec.) 1965. **7.** Girotti, M., Hauser, G. A.: *Praxis* 53:3 (Dec. 10) 1964. **8.** Baldwin, W. F.: *Can Med Assoc J* 89:566 (Sept. 14) 1963. **9.** Blazy, G.: *Toulouse Med* 64:625 (June-July) 1963. **10.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **11.** Bauer, H.: *Therapie der Gegenwart* 100:528 (Oct.) 1961. **12.** Suarez, J., *et al: Int Rec Med* 173:639 (Oct.) 1960. **13.** Monias, M. B., *et al: Md State Med J* 9:439 (Aug.) 1960. **14.** Kasdon, S. C., Morentin, B. O.: *J Int Coll Surg* 31:455 (April) 1959. **15.** Wager, H. P., Melosh, W. D.: *Quart Rev Surg Obst & Gynec* 15:30 (March) 1958. **16.** Herland, A. L., Lowenstein, A.: *Quart Rev Surg Obst & Gynec* 14: 196 (Dec.) 1957. **17.** Duncan, A. S.: *Brit Med J* 1:439 (Feb. 23) 1957. **18.** Peterson, W. F.: Unpublished report of 2,372 cases of puerperal constipation.

Purdue Frederick

©COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856

A8321 176676

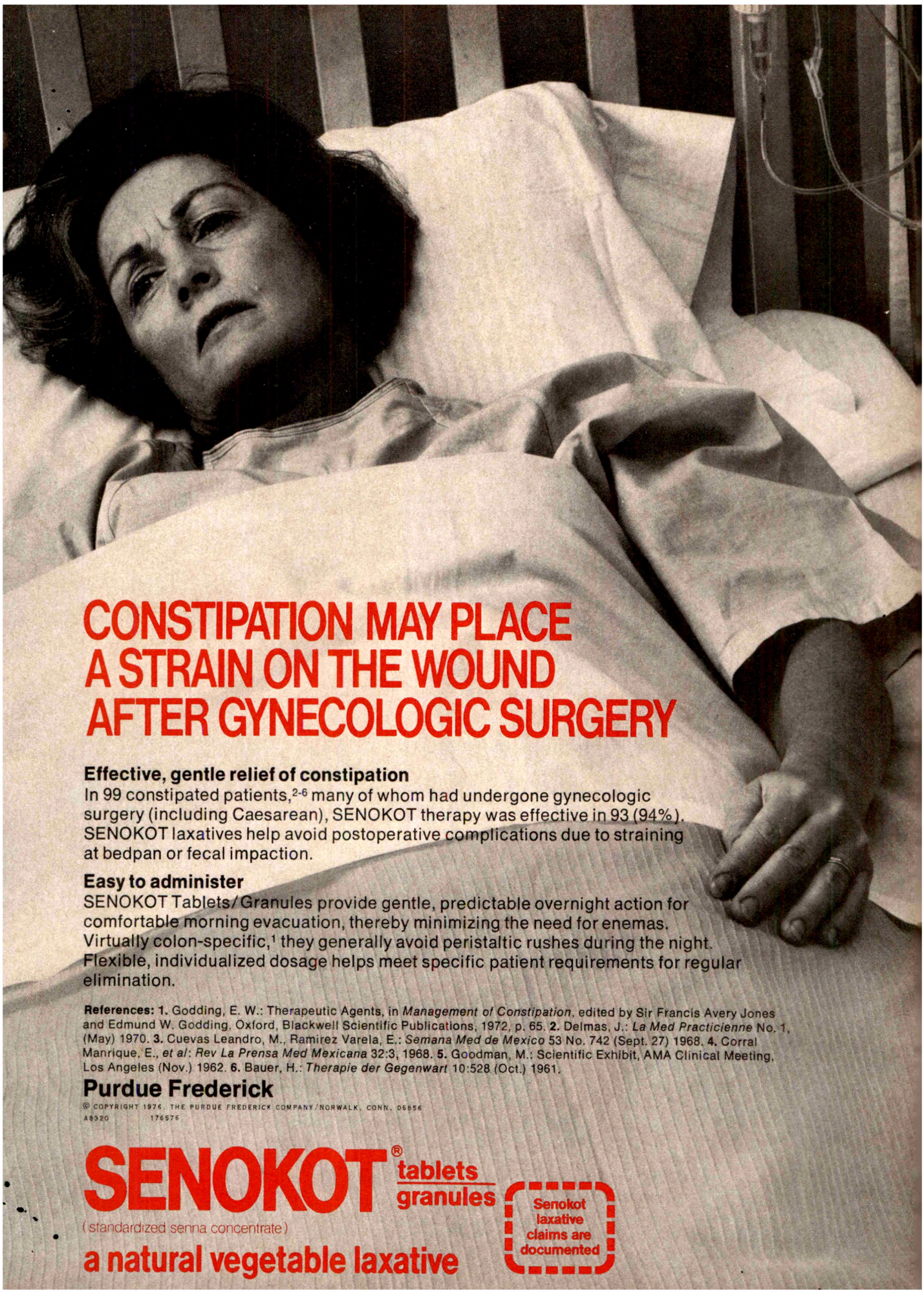
SENOKOT® tablets granules

(standardized senna concentrate)

a natural vegetable laxative

Senokot laxative claims are documented





CONSTIPATION MAY PLACE A STRAIN ON THE WOUND AFTER GYNECOLOGIC SURGERY

Effective, gentle relief of constipation
In 99 constipated patients,[2-6] many of whom had undergone gynecologic surgery (including Caesarean), SENOKOT therapy was effective in 93 (94%). SENOKOT laxatives help avoid postoperative complications due to straining at bedpan or fecal impaction.

Easy to administer
SENOKOT Tablets/Granules provide gentle, predictable overnight action for comfortable morning evacuation, thereby minimizing the need for enemas. Virtually colon-specific,[1] they generally avoid peristaltic rushes during the night. Flexible, individualized dosage helps meet specific patient requirements for regular elimination.

References: 1. Godding, E. W.: Therapeutic Agents, in *Management of Constipation*, edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 65. **2.** Delmas, J.: *La Med Practicienne* No. 1, (May) 1970. **3.** Cuevas Leandro, M., Ramirez Varela, E.: *Semana Med de Mexico* 53 No. 742 (Sept. 27) 1968. **4.** Corral Manrique, E., *et al*: *Rev La Prensa Med Mexicana* 32:3, 1968. **5.** Goodman, M.: Scientific Exhibit, AMA Clinical Meeting, Los Angeles (Nov.) 1962. **6.** Bauer, H.: *Therapie der Gegenwart* 10:528 (Oct.) 1961.

Purdue Frederick

© COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8320 176576

SENOKOT® tablets / granules
(standardized senna concentrate)
a natural vegetable laxative

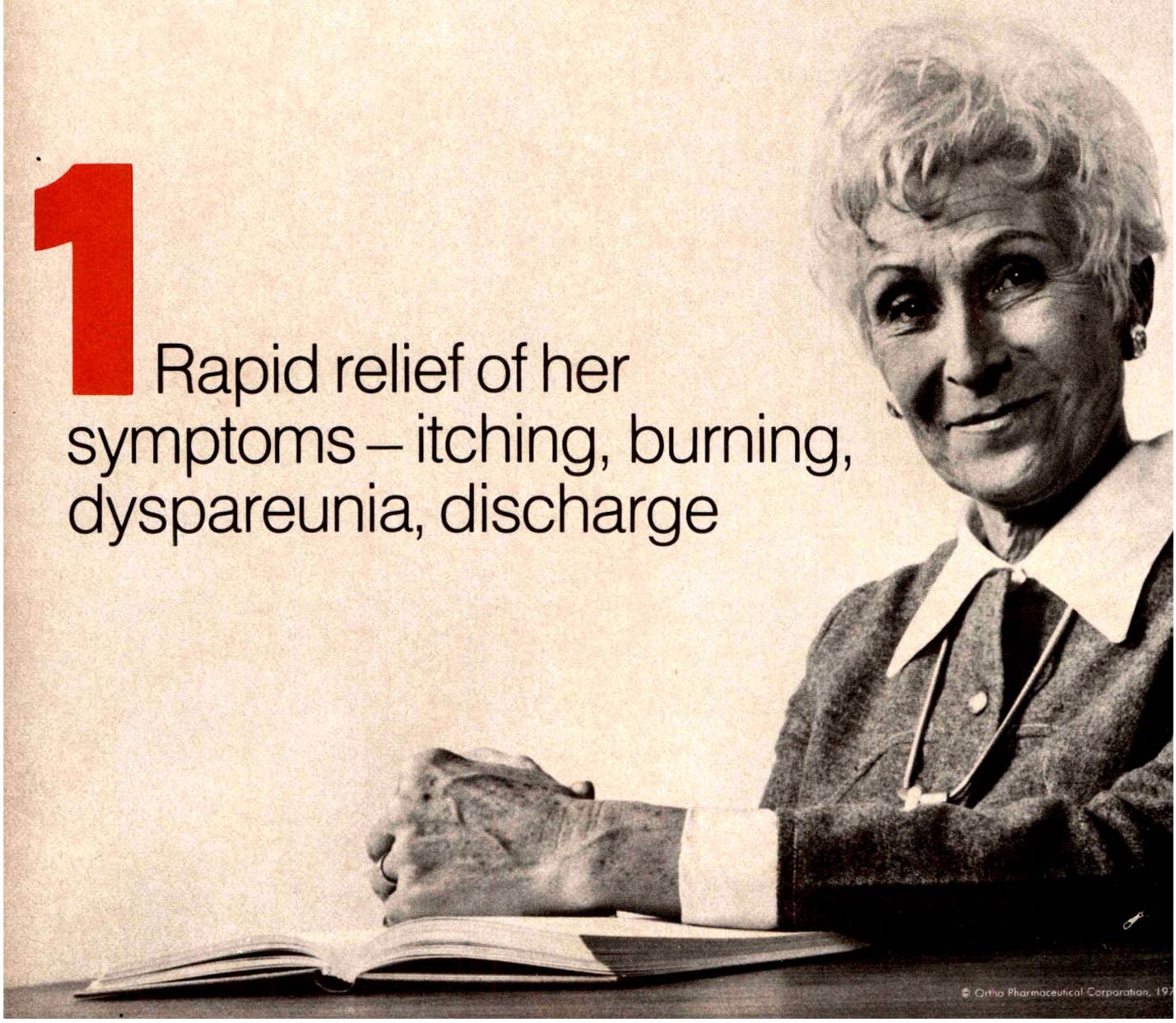
Senokot laxative claims are documented

Two reasons your atrophic vaginitis patient will really appreciate ORTHO Dienestrol Cream:

TRADEMARK

(dienestrol 0.01%)

1 Rapid relief of her symptoms – itching, burning, dyspareunia, discharge



© Ortho Pharmaceutical Corporation, 19

2 Provides economical relief of her symptoms that's easy on her pocketbook...an important consideration if she's on long-term maintenance therapy or a fixed income



Indications: Dienestrol Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases. *Contraindications:* Malignancies or precarcinomatous lesions of the vagina or vulva. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy. *Warning:* Vaginal adenosis has been reported in 30% to 90% of postpubertal girls and young women whose mothers received diethylstilbestrol or a closely related congener during pregnancy. This condition was found most frequently in those cases where DES had been given in early pregnancy (first 12 weeks). The significance of this finding with respect to potential for development of vaginal adenocarcinoma is unknown. Periodic examination of such patients is recommended. *Precautions:* In pruritus vulvae due to infectious conditions, the organism responsible for the infection should be treated with a specific agent. *Dosage:* One or two applicatorsful per day for one or two weeks, then gradually reduced to one-half initial dosage for a similar period. A maintenance dosage of one applicatorful, one to three times a week may be used after restoration of the vaginal mucosa has been achieved. *Supplied:* Available in 2.75 oz. (78 g) tubes with or without ORTHO* Measured-Dose Applicator.

*TRADEMARK

Ortho Pharmaceutical Corporation

INDEX TO ADVERTISERS

Abbott Laboratories
Iberet-500/Iberet-Folic-500 ____ 26, 27

Ayerst Laboratories
Dermoplast ____ Fourth Cover
Premarin Vaginal Cream ____ 36, 37, 38

Breon Laboratories Inc.
Fergon ____ 12

Browne Corporation
Endoscopy/Cystometry Monitors ____ 20

Burroughs Wellcome Co.
Empirin Compound with Codeine No. 3 ____ 4

Carnation Company
Instant Milk ____ 8

Dynatech Cryomedical Company
Dynafrost ____ 31

Hamot Medical Center
Classified ____ 45

Mead Johnson Laboratories
Ovcon ____ 15, 16, 17, 18

Medical College of Wisconsin
Postgraduate Course ____ 22

Merrell-National Laboratories
AVC ____ 6

Ortho Pharmaceutical Corporation
Dienestrol ____ 42, 43
Ortho-Novum 1/50 ____ 52
Sultrin ____ 32, 33

Purdue Frederick Company, The
Betadine Microbicides ____ 10
Betadine Perineal Wash ____ 53
Betadine Vaginitis Regimen ____ 24, 25
Senokot ____ 39, 40, 41

Reynolds Industries, Inc., R.J.
Classified ____ 14

Roche Laboratories
Azo Gantanol ____ 2, 3

Roerig, A Division of Pfizer Pharmaceuticals
Geopen ____ 34, 35

Schmid Laboratories, Inc.
Saf-T-Coil ____ 46

Searle & Co., G.D.
Flagyl ____ 54, Third Cover

Sonicaid, Inc.
Portable Fetal Heart Detector ____ 1

Stuart Pharmaceuticals, Division of ICI United States Inc.
Prenatals ____ 23

Syntex Laboratories, Inc.
Vagitrol ____ Second Cover, 1

University of Tennessee
Classified ____ 45

Winthrop Laboratories
Danocrine ____ 48, 49, 50, 51

Wyeth Laboratories
Lo/Ovral ____ 28, 29, 30
Ovral ____ 47

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

GYNECOLOGIC ENDOCRINOLOGIST

Applications are invited for a faculty position for a fully-trained and certified obstetrician-gynecologist with formal training or experience in reproductive endocrinology and/or infertility to join an active, aggressive and productive program. Send complete resume and letters of reference to: James R. Givens, M.D., Director, Div. of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee, Center for the Health Sciences, 800 Madison Avenue, Memphis, Tennessee 38163. An equal opportunity employer.

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 339, Erie, Pennsylvania 16512.

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION (Required by 39 U.S.C. 3685). 1. Title of Publication: AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. 2. Date of filing: October 1, 1976. 3. Frequency of issue: Semi-Monthly. 3A. No. of issues published annually: 24. 3B. Annual subscription price: $27.00. 4. Location of known office of publication: 11830 Westline Industrial Drive, St. Louis, Missouri 63141. 5. Location of the headquarters or general business offices of the publishers: Same as 4. 6. Names and complete addresses of publisher, editor, and managing editor: Publisher—The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141; Editor—John I. Brewer, M.D., 303 East Superior Street, Chicago, Illinois 60611; Managing editor—None. 7. Owner: The C. V. Mosby Company, a corporation, owner of publication, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. All of the stock of The C. V. Mosby Company is owned by Times Mirror Company, a corporation, Times Mirror Square, Los Angeles, California 90053. 8. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: None. 9. Not applicable to The C. V. Mosby Company.

10. Extent and nature of circulation	*Average no. copies each issue during preceding 12 months*	*Actual number of copies of single issue published nearest to filing date*
A. Total no. copies printed *(net press run)*	20,492	20,679
B. Paid circulation		
1. Sales through dealers and carriers, street vendors and counter sales	None	None
2. Mail subscriptions	19,370	18,990
C. Total paid circulation	19,370	18,990
D. Free distribution by mail, carrier, or other means, samples, complimentary, and other free copies	692	559
E. Total distribution *(Sum of C and D)*	20,062	19,549
F. Copies not distributed		
1. Office use, left over, unaccounted, spoiled after printing	430	1,130
2. Returns from news agents	None	None
G. Total *(Sum of E, F1 and 2—should equal net press run shown in A)*	20,492	20,679

11. I certify that the statements made by me above are correct and complete.

A. Jerome Freeland, *Journal Publisher*

12. In accordance with the provisions of this statute, I hereby request permission to mail the publication named in Item 1 at the phased postage rates presently authorized by 39 U.S.C. 3626.

A. Jerome Freeland, *Journal Publisher*



She's looking to you for answers. Reassure her.

Results of ten years' clinical experience with Saf-T-Coil® can help you provide the information she's seeking.

Saf-T-Coil is an IUD found comparable to the "pill" in use effectiveness.[1-3] Results of one of the longest investigations—a five-year study[2] in Florida clinics, based on 27,712 insertions and 541,248 woman-months of use—indicate: a low 0.8% *in situ* pregnancy rate, high 80% continuation rate, 11.9% expulsion rate and 8.0% removal rate. Subsequently, the investigators made Saf-T-Coil their "device of first choice."

Three Saf-T-Coil sizes ensure contraceptive effectiveness throughout her reproductive years: Saf-T-Coil Nullip 25-S for the nulliparous and young woman, Saf-T-Coil 32-S for the primiparous woman and Saf-T-Coil 33-S for the multiparous woman.

Saf-T-Coil Nullip 25-S, in particular, has proved to be a device well-suited to the woman with a small uterus. Results of a separate two-year study[1] in Florida clinics, based on 1,179 insertions and 9,750 woman-months of use, indicate a low 0.4% *in situ* pregnancy rate, relatively high 70% continuation rate, 11% expulsion rate and 19% removal rate—both considered acceptable in nulliparous patients. Insertions were easy and virtually painless, using the standard techniques and no anesthesia. And the Nullip 25-S rapidly accommodated to the shape of the uterine cavity—in contrast to the more rigidly designed devices,which force the uterus to conform. No serious complications were reported in this study.

Every Saf-T-Coil is made of inert plastic with no copper additives.

And with every Saf-T-Coil—Saf-T-Sound®—the sterile, disposable intrauterine probe that helps make fitting easier and more accurate.

Caution: Federal law restricts this product to sale by or on the order of a physician.
Contraindications: Should not be used in pregnancy or suspicion of pregnancy, suspicion of carcinoma, acute cervicitis, acute or subacute adnexal disease, fibroids, menorrhagia or unexplained bleeding.

1. Caraway, A. F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A. F. and Vaughn, B. J.: J. Reprod. Med. *10*:171, April 1973.
3. Hayes, O. J.: South. Med. J. *66*:254, Feb. 1973.

Sterile, inert plastic

Saf-T-Coil®



SCHMID LABORATORIES INC.
LITTLE FALLS NEW JERSEY 07424

Gonadoblastoma: Clinicopathologic correlation in six patients

H. OLIVER WILLIAMSON, M.D.
PAUL B. UNDERWOOD, JR., M.D.
ALBERT KREUTNER, JR., M.D.
J. FELIX ROGERS, M.S.
RAJESH S. MATHUR, PH.D.
H. RAWLING PRATT-THOMAS, M.D.
Charleston, South Carolina

Six patients with a total of nine gonadoblastomas are presented; three—and possibly a fourth—had dysgerminomatous overgrowth which was massive in two patients. Calcification detected by abdominal films was present in three sufficient for preoperative diagnosis. All patients were found to have a Y stem line on peripheral leukocyte chromosome cultures except one patient, who had a 46 XX/45 XO karyotype. She was found to have Y chromatin bodies in the germ cells of her tumor which was in a normal ovary found at exploration for an ectopic pregnancy. Three were found in virilized phenotypic females investigated for amenorrhea, and two for therapy of pelvic masses due to dysgerminomatous overgrowth. Y chromatin studies are reported on gonadal tissue.
(AM. J. OBSTET. GYNECOL. 126: 579, 1976.)

ON REVIEWING 14 tumors previously classified as dysgerminomas or arrhenoblastomas, Scully[1] found two tumors which were in part dysgerminomas but elsewhere were composed of tissues of sex-cord and mesenchyme origin (Sertoli or granulosa cells and Leydig or theca cells). In that work, he supplied the name "gonadoblastoma," feeling that it denoted the embryonic recapitulation by these tumors as well as being noncommittal as to the type of gonad from which they arose. Scully[2] remains a leading authority on these tumors, having personally reviewed microscopic slides on 17 published cases and 19 unreported cases while reviewing 101 tumors encountered in a total of 74 patients. This tumor equates with the gonocytoma III of Teter[3] and the mixed germ-cell tumors of Hughesdon and Kumarasamy.[4] We now summarize our clinical experience with six patients having gonadoblastomas and report on Y chromatin studies of their gonadal tissues.

From the Departments of Obstetrics and Gynecology and Pathology, Medical University of South Carolina.

Presented at the Thirty-eight Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. H. Oliver Williamson, Department of Obstetrics and Gynecology, Medical University of South Carolina, 80 Barre St., Charleston, South Carolina 29401.

Materials and methods

All patients were seen on referral for evaluation of amenorrhea or pelvic masses. However, Patient 4 was operated upon in an affiliated hospital by one of our resident physicians. Gonadal tissue was formalin fixed and thin sections were taken from paraffin blocks and stained for fluorescent Y bodies by the technique of Pearson and Babrow.[5] Where sections were too thick, digestion with viocase was carried out and thinner preparations made and similarly stained. Known positive controls were employed, and all staining was accomplished from the same batch of dye in 2 working days. Two patients were irradiated, receiving 2,500 rads via 15 cm. wide pelvic and 8 cm. wide abdominal para-aortic ports. A separate 8 cm. wide port was directed to the chest to include the mediastinum and left supraclavicular region. All patients are being maintained on interrupted therapy with conjugated equine estrogen and added medroxyprogesterone acetate in the latter half of each cycle. Table I summarizes the six cases.

Table I. Summary of six cases of gonadoblastoma

	Case 1	*Case 2*	*Case 3*	*Case 4*
Presenting symptoms	Amenorrhea	Amenorrhea	Amenorrhea and sterility	Rupt. rt. ectopic preg. Ovary removed due to infiam. process. Other ovary removed later
Medical history		Hepatitis, dyspareunia. Urinary tract infec.	Rapid growth over 8 wk. rt. adnex. mass	
Family history	Father died with ca. of lung. Fertile bro. and sis. No diabetes mellitus	? (reared in foster home)	Mother and MGM with genital carcinoma	
Marital status	M	M	M	M
Estrogen induced	+	+	+	NA
Weight (Kg.)	62	43	63	
Height (cm.)	167	156	161	
Span	171	157	162	
LS	87	79	80	
Bust	84	75	90	
Waist	64	63	70	
Hips	98	79	96	
Carrying angle	19°	17°	24°	
Palpable mass	0	0	+	0
Palpable nodes	0		0	0
Blood pressure (mm. Hg)	130/80	100/64	100/60	
Anomalies	Ectopic adrenal left mesovarian	Imperforate anus, sacral anomaly. Horseshoe kidney	Inguinal hernia	0
Intravenous pyelogram and abdominal film	Calcification	Horseshoe kidney	0	—
Therapy	Hyst. and bilat. S&G	Bilat. S&G	Hyst. and bilat. S&G	Hyst. and bilat. S&G
Survival since	1972	1973	1966	1972
Follow-up	Clitoromegaly persists. Hirsutism cleared	Clitoromegaly persists. Hirsutism cleared	Clitoromegaly persists. Hirsutism cleared.	
Gonad rt.	Streak with 2.5 cm. GBL. Y chromatin neg.	Streak with clusters of Leydig cells	Indeterminate with 4.2 cm. GBL and dysgerm. overgrow. Y chromatin neg.	4.5 cm. ovary with 2 cm. GBL. Y chromatin pos.
Gonad lt.	Streak with 0.5 cm. GBL. Y chromatin neg.	Indeterminate with 2 cm. GBL. Y chromatin pos.	Streak with 0.5 cm. GBL. Y chromatin neg.	2.5 cm. ovary

Results

All patients are surviving and well without evidence of residual disease as shown by physical examination and chest x-ray. No further statural growth has occurred, though all patients except No. 4 have experienced further development of secondary sex characteristics, including breast enlargement and deposition of fat in female distribution. The pathologic findings are the subject of a separate report.[6]

Fluorescent studies for Y chromatin were positive in the primitive germ cells, possibly representing dysgerminomatous overgrowth in a gonadoblastoma found in a normal ovary (Case 4), and also in the dysgerminoma portion of the largest (20 cm.) tumor. Y chromatin–positive cells appeared in clusters, whereas many other areas were negative for these bodies. They were not identified in Leydig cells nor in the granulosa-theca cells. Patient 4, a phenotypically normal female with 46 XX/45 XO peripheral leukocyte karyotype, had buccal smears positive for the X chromatin mass whereas the vaginal and blood smears were negative for Y chromatin, yet her tumor was Y chromatin positive.

Ovarian stroma was present in all gonads; however, the type of gonad could definitely be identified only in Patient 4, who had bilateral ovaries.

Patient 6, who is being reported since submission of our pathologic study, underwent right gonadectomy with removal of a 20 by 18 cm. mass in May, 1975. This was diagnosed as a dysgerminoma elsewhere, but later review revealed admixture throughout with gonadoblastoma. The left gonad was thought normal at surgery and was left in situ. On referral, x-ray studies

Case 5	Case 6
Mass on precollege exam.	Abd. pain and incr. abd. girth 7 wk. and secondary amenorrhea
MGF+ for ca. of colon. No diabetes mellitus	GF died of ca. 2 bro. & sis. normal—one 9 lb. 2 oz. at birth. No diab. mellitus
S	S
+ (post surgery)	NA
46	44
168	164
165	159
84	84
81	75
66	60
86	80
13°	17°
++	+++
0	+++
88/50	105/65
0	Occult spina bifida, low hair line
Calcification	Calcification, left
Bilat. S&G, x-radiation 1975	Hyst., bilat. S&G x-radiation 1975
Indeterminate with 14 cm. dysgerminoma	Indeterminate with 20 cm. GBL with dysgerm. overgrowth. Y chromatin pos.
Indeterminate with 6 cm. GBL and dysgerm. overgrowth. Y chromatin neg.	Indeterminate with 1 cm. GBL. Y chromatin neg.

showed left gonadal calcification leading to preoperative diagnosis. The following month, the patient underwent hysterectomy, left gonadectomy, and resection of a 2 cm. para-aortic lymph node which was negative for malignancy. However, suspicious nodes measuring to 4 cm. extended to the level of the diaphragm. Because of these findings, the patient was treated with x-radiation. The right gonad was 1 by 0.7 by 0.7 cm., gritty, and gray-tan. The uterus was 7.2 by 5.1 by 1.8 cm. with myometrium to 0.9 cm. and endometrium to 0.1 cm. in thickness. Microscopically, the left gonad was a typical gonadoblastoma with immature germ, granulosa, and Leydig cells. Peripheral blood yielded an XY karyotype and smears were positive for Y chromatin. Buccal and vaginal smears were X chromatin negative. Plasma follicle-stimulating hormone (FSH) and luteinizing hormone (LH) after resection of the right dysgerminoma and gonadoblastoma but before that of the left gonadoblastoma, were 36 and 68 mI.U. per milliliter, respectively. Plasma estradiol was 7.9 ng. per 100 ml. preoperatively and 8.4 at operation, with venous plasma from gonadoblastoma being 26.5 ng. per 100 ml. Postoperative peripheral levels were 5.6 mg. per 100 ml. Preoperative plasma testosterone was 53 ng. per 100 ml. and postoperative 19 ng. per 100 ml., whereas levels from the gonad were 277 ng. per 100 ml. Human chorionic gonadotropin was present—5.6 ± 0.1 mI.U. per milliliter beta subunit (courtesy of Charles B. Hammond, M.D.)—although quantitative urinary HCG was negative.

Comment

Microscopic calcification in gonadoblastomas is such a common finding that it has been utilized as a marker for preoperative diagnosis. Although calcification was present in all except one of our patients, it was insufficient for diagnosis by routine abdominal films in all but three, suggesting that it needs to be extensive or confluent to be evident on such films. Furthermore, we have seen an isolated cluster of phleboliths in a patient with gonadal dysgenesis mimic the calcification of gonadoblastoma. Also, a calcified corpus albicans or uterine myomata could be confused. Detection of these lesions by palpation also can be difficult, as many are quite small and they may be fixed high in the pelvis, as in our first case. Lesions located in streaks may be extremely small and conceivably overlooked at laparoscopy. This small series would support the well-known concept that streaks should be removed in patients showing a Y stem line. If no gonad is found on visualization of the peritoneal cavity, then retroperitoneal and groin exploration may be in order.

We have obtained alkaline phosphatase determinations on each of our patients seen preoperatively because of the association of elevated alkaline phosphatase activity in undifferentiated embryonic cells[7] and having seen significant elevation in peripheral levels in one patient with massive dysgerminoma who had normal levels the day after resection. However, it has not proved useful in identifying patients with germ-cell tumors in association with gonadoblastomas in our series.

Gonadoblastomas in general are not considered malignant in that typical gonadoblastomatous elements have never been shown in metastatic foci. However, dysgerminomatous overgrowth with the possibility of metastases is ever present, as indicated by such overgrowth in three and possibly four of our patients.

Accordingly, lymphangiography would seem especially desirable since metastases of dysgerminomas are usually by the lymphatic route along the gonadal vasculature. Accordingly, positive nodes might be high in the para-aortic chain with negative pelvic nodes. Reports of lymphangiography in association with gonadoblastomas are conspicious by their absence, indicating difficulty or reluctance to obtain the procedure. Also, false-positive reports are well known.

Human chorionic gonadotropin (HCG) testing is of prognostic importance. If positive for the beta subunit then one would expect concomitant choriocarcinoma. Yet, recent findings of testicular production of HCG might be extrapolated to account for the low levels of this hormone detected in our last patient.[8] The finding of gonadoblastoma at ectopic pregnancy in Case 4 can only be classed as fortuitous and here the HCG could confound the issue. It has been suggested that a positive pregnancy test could be due to increased LH levels and in turn if such elevated levels are inhibited by exogenous estrogen that a better prognosis exists.[9]

Had the basic principle of thoroughly investigating amenorrhea by the age of 18 been followed, three of our cases would probably have been detected earlier. Yet, the two with massive dysgerminomatous overgrowth would have been missed were this the only indication for evaluation. Also, this would even be more likely since the two had experienced spontaneous breast development and one even had normal menses, though she had lapsed into amenorrhea.

There appears to be no specific physical appearance associated with gonadoblastomas, though the impression is gained that the gynecologist is most apt to see a phenotypic female with some signs of virilization. It seems rare in patients with a Turner phenotype. None of ours have the full Turner phenotype, yet four had carrying angles greater than 15° and one had a suggestion of low posterior hairline. This disorder has been seen in association with pure gonadal dysgenesis,[10] mixed gonadal dysgenesis,[11] and true hermaphroditism,[12] as well as in phenotypically normal males and females.[2] It seems to occur sufficiently frequently in relatives to warrant interrogation regarding family history of amenorrhea.[13–16]

Delayed bony development has been noted,[17] yet steroid production seems sufficient to close epiphyses at the normal time in all of our patients over the age of 20. The finding of a history of hepatitis in two of our patients seems coincidental, yet the finding of extensive family histories of cancer in all patients from whom histories were obtained may be significant. Investigation of carbohydrate metabolism in our patients showed no evidence of diabetes, and only one patient had a positive family history (an aunt of Patient 3). This is in contradistinction to gonadal dysgenetics having the Turner phenotype.[18]

The matter of breast tissue development in XY individuals with gonadal dysgenesis was explored by Cantu and associates.[17] Their patient had calcium present in a gonad which was likely a gonadoblastoma, and their study suggested that the breast tissue converted androgens to estrogens. Such a mechanism need not be invoked, for significant levels of estradiol were detected in venous blood from the gonadoblastoma in our Case 6 and significant amounts of estrogen have been detected in three of our patients. MacKay and associates[19] commented on the absence of virilization in some individuals with elevated testosterone and suggested the possibility that the situation may be comparable to that in testicular feminization syndrome (absent intracellular androgen receptor).[19] We rather suspect that this simply represents considerable variation in end-organ responsiveness.

Bilaterality of these tumors occurs so frequently that thorough investigation and even removal of the contralateral gonad would seem desirable in most. Yet, in Patient 4 with ectopic pregnancy, no tumor was found in the contralateral gonad after extensive search. Where massive dysgerminomatous overgrowth has occurred an associated gonadoblastoma might easily be overlooked. X-ray of the tumor proper and serial sectioning with care being taken to look for gritty areas may reveal gonadoblastomatous areas. However, this might be veiwed simply as an academic exercise, for the treatment remains the same as for uncomplicated dysgerminoma unless concomitant choriocarcinoma exists. Then it is probably not helpful due to the bleak outlook. Also, a gonadoblastoma in a phenotypically normal individual is unlikely to be detected unless the gonad is carefully sectioned, for in our Case 6, a gonadoblastoma was thought a normal ovary by gross inspection at the time of removal of a contralateral tumor. A number of gonadoblastomas have been found retrospectively, including those of the original report.[1] We are of the opinion that, were tissue available in most patients having dysgerminomas in association with pseudohermaphroditism, gonadoblastomas would be found in a significant number. Scully[1] cited the Sailer[20] case of dysgerminoma with granulosa cells intermixed, but this has been questioned by Hughesdon and Kumarasamy.[4] Unfortunately, only one slide of this tumor remains in our files; it does not show the sections photographed by Dr. Sailer but shows only dysgerminomatous elements with heavy lymphocytic infiltration. This patient remains alive and well.

No unanimity of opinion regarding therapy for gonadoblastomas exists, and this state is likely to persist, for the staff of no one institution is likely to gain

sufficient experience to dictate what is the proper mode of therapy. Our feeling is, where simple uncomplicated gonadoblastomas exist, that simple excision is sufficient and that the uterus may be left in if withdrawal bleeding for reinforcement of femininity is thought desirable. However, this must be balanced against the possibility of malignancy in that increasing reports of endometrial carcinoma in association with exogenous estrogen administration are appearing. If the uterus is left in situ, then it is felt that estrogen should be given in an interrupted fashion and be accompanied by progestogen. The matter of a possible gonadal transplant must be discounted, for this would call for immunosuppression, hence unroofing the possibility of malignancies in those already so predisposed. Selection of patients for radiotherapy where dysgerminomatous overgrowth has occurred is also not settled. Mitotic activity is notoriously unreliable in predicting the behavior of these neoplasms. Even lymphatic invasion in the gonad does not necessarily carry a bad prognosis. However, we feel, if dysgerminomatous overgrowth to 5 cm. or more exists, but there is no evidence of clinical spread, either locally or by lymphatics, that irradiation to the pelvic and para-aortic lymph nodes to the level of the diaphragm should be undertaken with a 15 by 15 cm. pelvic and 8 cm. wide para-aortic port to the level of 2,500 rads. If para-aortic nodes are positive, then a second port is added to encompass the mediastinum and left supraclavicular region. No irradiation would be given to a lesion smaller than 5 cm. without evidence of local extension or lymph node metastases. The possibility exists of finding a fertile female, such as our Patient 4, who has a normal contralateral gonad. Theoretically, one could suture the normal gonad outside of the field for irradiation and radiate only the side of the pelvis involved, in the hope of preserving fertility. Yet the knowledge of the bilaterality of these tumors led to our removing the contralateral gonad in this patient.

The occurrence of a dysgerminoma alone or dysgerminomatous overgrowth in a gonadoblastoma on the right in three and probably four of our patients agrees with the predilection of dysgerminomas on the right as reported by others.[20] Gonadoblastomas were found in all of the left gonads of our patients with the exception of the one with the ectopic pregnancy (Case 4). Only one of our patients had a dysgerminoma on the left, yet she had a larger one on the right. The predominance of dysgerminomas on the right remains inexplicable; however, it may represent a phylogenetic throwback. The hen ordinarily has a right gonadal streak and a functioning left ovary. If the left ovary is removed, then the gonadal streak will develop abnormally, usually along testicular lines. The thought persists that the absence of responsive adult gonadal tissue causes an increased pituitary gonadotropin secretion with stimulation of primordial tissue ultimately leading to tumor formation.[4] If this be so, then one wonders why all patients with gonadal dysgenesis do not experience tumor growth. Yet those with the Y chromosome do seem so predisposed, being comparable to the development of seminomas of the undescended testicle. Also enigmatic is the matter of the relatively low-grade malignancy of dysgerminomas of the ovary (and apparently also gonadoblastomas) as contrasted with the microscopically identical lesion of the testicle. If elevated gonadotropins are truly causative, the gonadotropin suppression doses of estrogen probably should be advocated in substitutional therapy of all patients with gonadal dysgenesis.

The finding of pregnancy in one of our patients is distinctly unusual, and yet is not totally unexpected when one considers that true hermaphrodites have been noted to have simultaneously active spermatogenesis and evidence of ovulation. Accordingly, one might expect tissues of a primitive type to interfere even less with gonadal function. In the initial reporting of this patient,[21] it was noted that she was unusual in that apparently she had the development of a gonadoblastoma in the absence of a Y stem line. The more recent finding of Y chromatin bodies in her tumor still supports the thesis that patients with a Y stem line should have streaks removed because of the propensity for tumor formation. Yet it points out the difficulty in detecting such a Y stem line, for it may be present in only a small clone of cells. The finding of clusters of Y chromatin–positive cells would support such a clone theory. Where virilization is evident, or Y chromatin bodies are detected, the decision is simplified. Yet other patients will exist where a Y stem line will be exceedingly difficult to detect—conceivably only in the gonad. Accordingly, should one explore a patient and streaks be found, it would seem prudent to proceed with their removal in spite of the fact that one may occasionally find a few follicles suggesting the possibility of fertility.

REFERENCES

1. Scully, R. E.: Gonadoblastoma: A gonadal tumor related to the dysgerminoma (seminoma) and capable of sex-hormone production, Cancer **6:** 455, 1953.
2. Scully, R. E.: Gonadoblastoma, a review of 74 cases, Cancer **25:** 1340, 1970.
3. Teter, J.: A mixed form of feminizing germ cell tumor (gonocytoma II), AM. J. OBSTET. GYNECOL. **84:** 722, 1962.

4. Hughesdon, P. E., and Kumarasamy, T.: Mixed germ cell tumours (gonadoblastomas) in normal and dysgenetic gonads, Virchows Arch. [Pathol. Anat.] **349:** 258, 1970.
5. Pearson, P. L., and Babrow, M.: Technique for identifying Y chromosomes in human interphase nuclei, Nature **226:** 78, 1970.
6. Garvin, J. A., Pratt-Thomas, H. R., Spector, M., Spicer, S. S., and Williamson, H. O.: Gonadoblastoma: Histologic, ultrastructural, and histochemical observations in five cases, AM. J. OBSTET. GYNECOL. **125:** 459, 1976.
7. Josso, N., Nezelof, C., Picon, R., Grouchy, J., Dray, F., and Rappaport, R., Gonadoblastoma in gonadal dysgenesis: A report of two cases with 46, XY/45, X mosaicism, J. Pediatr. **74:** 425, 1969.
8. Braunstein, G. D., Rasor, J., and Wade, M. E.: Presence in normal human testes of a chorionic-gonadotropin-like substance distinct from human luteinizing hormone, N. Engl. J. Med. **293:** 1339, 1975.
9. Rockwell, W., (edited by Tihen, W. S.): Dysgerminoma and gonadoblastoma, J. Kansas Med. Soc. **67:** 289, 1966.
10. Farber, M., Palmer, P. E., and Bull, M. J.: Pure gonadal dysgenesis with bilateral gonadoblastomas, Obstet. Gynecol. **42:** 186, 1973.
11. Kariminejad, M. H., Movlavi, M. A., Nasserghodssi, M. A., Ghafoorzadeh, D., and Behjatnia, Y.: Gonadoblastoma associated with mixed gonadal dysgenesis, AM. J. OBSTET. GYNECOL. **113:** 410, 1972.
12. Park, I. J., Pyeatte, J. C., Jones, H. W., and Woodruff, J. D.: Gonadoblastoma in a true hermaphrodite with 46,XY genotype, Obstet. Gynecol. **40:** 466, 1972.
13. Cohen, M. M., and Shaw, M. W.: Two XY siblings with gonadal dysgenesis and a female phenotype, N. Engl. J. Med. **272:** 1083, 1965.
14. Talerman, A.: Gonadoblastoma and dysgerminoma in two siblings with dysgenetic gonads, Obstet. Gynecol. **38:** 416, 1971.
15. Anderson, C. T., and Carlson, I. A.: Elevated plasma testosterone and gonadal tumors in two 46,XY sisters, Arch. Pathol. **99:** 360, 1975.
16. Frasier, S. D., Bashore, R. A., and Mosier, H. D.: Gonadoblastoma associated with pure gonadal dysgenesis in monozygous twins, J. Pediatr. **64:** 740, 1964.
17. Cantu, J. M., Olivera, E., Gonzalez, D., Hidalgo, F., Gonzalez, M., and Gallegos, A. J.: A possible explanation for spontaneous breast development in XY gonadal dysgenesis, Ann. Endocrinol. **33:** 517, 1972.
18. Engel, E., and Forbes, A. P.: Cytogenetic and clinical findings in 48 patients with congenitally defective or absent ovaries, Medicine **44:** 135, 1965.
19. MacKay, A. M., Pettigrew, N., Symington, T., and Neville, A. M.: Tumors of dysgenetic gonads (gonadoblastoma): Ultrastructural and steroidogenic aspects, Cancer **34:** 1108, 1974.
20. Sailer, S.: Ovarian dysgerminoma, Am. J. Cancer **38:** 473, 1940.
21. Pratt-Thomas, H. R., and Cooper, J. M.: Gonadoblastoma with tubal pregnancy, Am. J. Clin. Pathol. **65:** 121, 1976.

Discussion

DR. JOHN BOTTOMY, Atlanta, Georgia. The author has presented six well-documented cases of gonadoblastoma, five of which contain the genotype XY chromosomes and one case in which no Y chromosomes could be demonstrated. Several other cases of gonadoblastoma have been reported in the literature having no Y chromosomes in their genotype. One of these patients conceived and was delivered of a normal infant; this case corresponds to that of the patient in this series with ectopic pregnancy. One possible explanation given is that of streak and ovary similar to the streak and testes occasionally encountered.

In the discussion of these cases, Dr. Williamson has correlated many of the current concepts and theories in the literature with the findings in the six cases presented, and the comparison of these findings gives rather a complete picture of our knowledge of these tumors. The association and interrelationship of the gonadoblastoma with other more serious embryonic tumors and the part they may play in either stimulating or possibly even producing these germ-cell tumors still leave many unanswered questions which only the reporting of similar tumors will help clarify. In a previous paper co-authored by Dr. Williamson, histologic, ultrastructural, and histochemical studies were carried out on five of these six patients in an attempt to determine the possible role in influencing the course of these tumors.

Gonadoblastoma is an accepted and established sex-chord tumor arising in a dysgenetic gonad with the Y chromosome nearly always a prerequisite for gonadal malignancy. Despite the infrequent occurrence of these tumors without a Y chromosome it is still the patient with gonadal dysgenesis and Y chromosome pattern about whom we worry most—statistically in regard to germ-cell tumors.

In a synopsis of authors reporting groups of patients collected by Schellhas, a mean incidence of 25 per cent malignant germ-cell tumors was found. The prognosis appears to be that of the germinomatous part with frequent overgrowth of dysgerminomatous elements which have been found to metastasize. A close interrelationship with the more malignant germ-cell tumors such as embryonal carcinoma and choriocarcinoma is not an infrequent finding. The component makeup of the gonadoblastoma seems almost to be a stepping stone to the more malignant germ-cell tumors, whether by inherent potential or dependence upon hormonal stimulation. With the above inference of a relative malignant potential, some rules of clinical management seem evident.

The gonadal dysgenic patient without demonstrable Y chromosomes in the absence of a palpable mass is probably in a low-risk category and may not require exploratory laparotomy with laparoscopic evaluation a possibility. Conversely, the patient with gonadal dysgenesis and Y chromosome should be explored, as a diagnosis by other surgical procedures may be difficult due to the sometimes inconspicuous nature of gonadal streaks and abnormal location of the gonads. To insure not overlooking a gonadoblastoma, patients

with Turner's syndrome or Turner's mosaic, primary or secondary amenorrhea extending into the latter teens, virilism, clitoral hypertrophy, or other symptoms suggestive of dysgenetic gonads should be scanned genetically for Y chromosomes in addition to the usual laboratory endocrine determinations. Recent improvement in genetic culturing techniques makes chromosomal determination with bilateral buccal smear and lymphocyte culture from peripheral blood capable of detecting the Y chromosome with considerable accuracy, aside from determining the extent of operative procedure carried out, and evaluating the malignant potential of the dysgenic gonad. Three cases referred to the Emory University Clinic between 1970 and 1975 well illustrate the malignant potential, inadequacy of primary procedure, and difficulty in diagnosis of these tumors.

The first case was that of a 26-year-old black woman with history of primary amenorrhea and infertility until 19 years of age. Cyclic hormone therapy produced intermittent uterine bleeding over the next 5 to 6 years, at which time a left adnexal mass was discovered. A mass diagnosed as dysgerminoma was removed from the left adnexal area. Six months later a second dysgerminoma was removed from the right adnexal region, in addition to a recurrence in the left side. Pelvic radiation was instituted and the patient was referred to our Oncology Service. Genetic evaluation revealed the patient to have XY genotype, and review of microscopic slides established the diagnosis of gonadoblastoma, dysgerminoma, and choriocarcinoma. The uterus was removed as was a mass metastatic to the cul-de-sac which had extensive areas of embryonal carcinoma. Repeated courses of chemotherapy have kept this patient alive 2 years after the original diagnosis and treatment at time of her referral elsewhere. Genetic evaluation prior to the original procedure would have saved two subsequent laparotomies and possibly improved her prognosis and diagnosis. Pathologic recognition of the original tissue could have instituted more radical management at an earlier date.

The second case was that of an 8-year-old phenotype female, explored because of a large mass thought to be an appendiceal abscess and diagnosed pathologically as a dysgerminoma and choriocarcinoma. Early pelvic recurrence of this tumor prompted her referral to our Oncology Service and review of her initial slides revealed a gonadoblastoma, an endodermal sinus tumor, and choriocarcinoma. Despite radiation therapy and chemotherapy the patient died 1 year after initial lapartomy.

The third case was that of a 5-year-old female with a shield type chest, blue sclera, hypocanthal folds, a flat and broad face, slightly elevated blood pressure, and a diagnosis of coarctation of the aorta. She was referred to the urologic service because an intravenous pyelogram revealed a malrotation of the kidney and was therefore managed on this service. The patient, though not a classical Turner's syndrome, was thought to be a variant mosaic, not a classic 45 X. Barr body count was less than 1 per cent and familial pedigree was negative for any genetic abnormality. Buccal smear was positive for Y chromosome bodies and peripheral lymphocyte culture revealed the XY chromosome, though they were present in a lower percentage than usually seen in males. An exploratory laparotomy revealed bilateral streak ovaries and a small uterus with rudimentary tubes. The streak ovaries were biopsied and frozen section at the time of surgery revealed no tumor. Review of fixed sections, however, revealed a gonadoblastoma on the right and bilateral streak ovaries. This finding necessitated a second laparotomy at which time both streaks were removed without the uterus. Removal of dysgenetic gonads allowing a uterus to remain in a phenotype female with male genotype does not appeal to me as a gynecologist. The patient probably will eventually desire hormone support and the uterus remains as a potential bleeding organ and possible future source of endometrial cancer. Numerous gonadoblastoma case reports occurring in the pediatric as well as the gynecologic literature reveal that many of the younger patients are being managed by urologists and pediatric surgeons instead of physicians in our specialty interested in pediatric gynecology.

Clinical experience with the copper-7 intrauterine contraceptive device

A preliminary report

WILLIAM A. NEBEL, M.D.
JOHN L. CURRIE, M.D.
RICHARD E. LASSITER, M.D.
Chapel Hill, North Carolina

There have been 203 copper-7 IUD insertions performed in 199 women. The data from 2,230 woman-months of use have been analyzed and compared with other published reports. The copper-7 IUD was an acceptable contraceptive method in regard to effectiveness, continuation, and lack of serious complications. (AM. J. OBSTET. GYNECOL. 126: 586, 1976.)

IN 1969 Zipper and associates[1] first proposed the addition of metallic copper to enhance contraceptive effectiveness of the intrauterine device (IUD). Later Zipper and associates[2] reported a reduction in pregnancy rate to zero when 200 sq. mm. of copper wire were added to the "T" IUD. A copper-containing IUD, the copper-7 (CU-7), was subsequently developed which also contains 200 sq. mm. of exposed metallic copper surface. This is currently the only available copper-containing IUD. Low pregnancy rates with the CU-7 IUD have been reported by Bernstein[3] (1.1 per cent), Newton[4] (1.1 per cent), and Shaila[5] (0.6 per cent) and their colleagues. Because of the small size of these devices, they are thought to be more suitable for nulliparous women.[8] It has been stated that the copper-7 IUD is no more effective than noncopper IUD's, but it is easier to insert and associated with less bleeding.[6] Hefnawi[7] documented that the copper IUD's caused less menstrual blood loss than the noncopper IUD's. The encouraging reports of increased effectiveness with the copper-7 IUD have been tempered by reports of associated morbidity. Mishell[8] emphasized the risk of cervical perforations (two per 4,000 insertions) as well as uterine fundal perforations (one per 376 insertions). If an intra-abdominal perforation occurs with a copper IUD, the IUD should be removed as it can cause a severe reaction within the peritoneal cavity.[9] Less serious problems such as ecchymatoid skin eruptions[10] have been reported. Fatal complications associated with the IUD during pregnancy have been published but none was associated with the copper-7 IUD.[11]

In April, 1974, a study was begun to evaluate this contraceptive method. Due to the warnings of possible complications mentioned above, it was felt that safeguards regarding its use were appropriate. Therefore an ongoing analysis of all of our patients who had selected the copper-7 IUD was established—both to insure the patient's well being and for investigative purposes. This presentation details the experience with the copper-7 IUD.

Materials and methods

Patients who selected this form of contraception were counseled regarding its effectiveness, limitations, and complications. All insertions were performed by one of three authors only during the menstrual period or at the 6 weeks postpartum or postabortal visit (Table I).

A uniform technique for insertion was utilized. After bimanual pelvic examination and cervical visualization, the cervix and vagina were cleaned with a 1:750 solution of benzalkonium chloride. A single-tooth tenaculum was applied to the anterior cervical lip and traction exerted toward the introitus. Uterine sound-

Presented as official guest at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. William A. Nebel, Chapel Hill Ob. Gyn. P.A., Conner Drive Professional Building, Chapel Hill, North Carolina 27514.

Table I. Time of first insertion

	No.
During menstrual period	139
Six weeks post partum	56
Six weeks after abortion	4
Total	199

Table II. IUD insertions, April, 1974, to December, 1974

	No.
First insertions	199
Reinsertions	4
Total	203
Woman-months of use	2,230
Lost to follow-up	4 (2%)

Table III. Demographic data

	No.	*Per cent*
Age (yr.):		
19 or less	1	0.5
20-30	171	86.0
30 or more	27	13.5
Total	199	100
Gravidity:		
0	68	34
1-2	120	60
2 or more	11	6
Total	199	100

ing to determine the depth and axis of the endometrial cavity preceded insertion of the copper-7 IUD. IUD insertion was performed by forcing the copper-7 IUD within its inserter, positioning the inserter so that the IUD end was at the top of the endometrial cavity, and withdrawing the inserter sheath back over the push-rod. In this fashion the copper-7 IUD unfolded high in the endometrial cavity and was not ejected from the inserter. Following insertions uterine sounding was performed in order to assure that the copper-7 IUD was high in the endometrial cavity. Patients were then instructed to locate the copper-7 IUD string and given a 2 month follow-up appointment. Additionally they were informed, and given written instructions, regarding the recommended 2 year effectiveness limitations.

Results

A total of 203 copper-7 IUD insertions were carried out in 199 patients between April, 1974, and December, 1974 (Table II). A total of 2230 woman-months of use have been accumulated. Other than four patients lost to follow-up, all patients have had at least a 12 months' experience with this IUD. As indicated in Table III, most women (86 per cent) were in the third decade of life. Approximately two thirds of the women had been previously pregnant (Table III). Women selecting this type of contraception had considerable prior contraceptive experience (Table IV). With the use of Tietze's[12] guidelines, net cumulative event and closure rates were determined (Table V). There were no expulsions following repeat insertions despite a 12.2 per cent first expulsion rate. Unacceptable uterine bleeding was the reason for removal in only eight patients (Table VI). Three patients encountered problems, one with transient acne and two with salpingitis. In one of the patients with salpingitis the diagnosis was confirmed by laparoscopy 1 month after IUD insertion. The culpability of the Cu-7 IUD in this process is unsure since additionally regional enteritis was diag-

Table IV. Prior contraceptive experience

No. of agents used	*No. of patients*	*Per cent*
None	6	3
One	82	41
Two	60	30
Three	31	16
Four or more	20	10
Total	199	100

Table V

Type of termination	*Rate per 100 women*
Events:	
Accidental pregnancies	1.6
First expulsions	12.2
Later expulsions	0.0
Removal for medical reasons	14.7
Removal for personal reasons	2.3
Closures:	
Accidental pregnancies	1.6
First expulsions	2.1
Later expulsions	0.0
Removal for medical reasons	14.7
Removal for personal reasons	2.3
Total closures	20.7
Active at end of first year	79.3

Table VI. Reasons for removal

	No.	*Per cent*
Unacceptable uterine cramping	13	45
Unacceptable uterine bleeding	8	27
Planned pregnancy	4	14
Other medical	2	7
Other personal	2	7
Total	29	100

Table VII. Net cumulative event and continuation rates per 100 Cu-7 users

	Accidental pregnancy	*Expulsion*	*Removal*	*Continuation rates*	*Insertions*	*Woman-months of use*
This study	1.6	12.2	17.0	79.3	203	2,230
Shalia et al.[5] (9 mo.)	0.6	17.1	8.4	73.9	400	2,555
Bernstein et al.[3]	1.1	4.1	12.4	Not available	186	1,693
Newton et al.[4]	1.1	6.7	3.0	93.9	342	1,197

nosed by radiologic examination. The other patient had used a Dalkon shield IUD which had been removed in 1973 for suspected salpingitis. This episode of salpingitis occurred after 5 months' use of the Cu-7 IUD. Both patients were treated with IUD removal and high doses of parenteral antibiotics. Both had good clinical response to therapy and have had no apparent sequelae.

There were no uterine perforations. Four patients with no IUD string visible at the external os did require additional evaluation to accurately determine the position of the IUD's. Procedures recommended by Ansari[13] were employed but did not confirm proper intrauterine positioning of these IUD's. Therefore hysterography was utilized in two patients and colposcopy in the other two patients to diagnose the intrauterine location of these four IUDs. Colposcopic examination allowed visualization of the IUD strings high in the endocervical canal.

Comment

The 98 per cent follow-up rate reflects the reliability of this study population. All the patients were informed at the time of insertion that follow-up would be necessary. Table VII compares the results of this study with those of other investigators who have reported on the copper-7 IUD. The pregnancy rate (1.6 per cent) is acceptable, as is the continuation rate of almost 80 per cent. The authors feel that these figures reflect proper patient selection and insertion timing combined with meticulous insertion techniques. There were no serious postinsertion problems with the possible exception of the two patients with salpingitis. With prompt removal of the IUD and vigorous antibiotic therapy, both patients recovered. There was not a definite cause-and-effect relationship between the salpingitis and the copper-7 IUD. The 12.2 per cent expulsion rate is rather high but there were no subsequent rejections following reinsertion.

Due to the length of time of this evaluation, the possibility of greater risk with the need to change the Cu-7 every 24 months[9] has not been addressed. Better information pertinent to this important question may become available with continued use of this form of contraception.

In summary, initial clinical experience in a private practice situation indicates that women with multiple prior contraceptive experiences have accepted the copper-7 IUD as a contraceptive method. Follow-up has been favorable regarding effectiveness, continuation, and lack of serious complications.

REFERENCES

1. Zipper, J. A., Tatum, H. J., Pastene, L., Medel, M., and Rivera, A.: Am. J. Obstet. Gynecol. **105:** 1274, 1960.
2. Zipper, J. A., Tatum, H. J., Medel, M., Pastene, L., and Rivera, M.: Am. J. Obstet. Gynecol. **177:** 602, 1973.
3. Bernstein, G. S., Israel, R., Seward, P., and Mishell, D. R., Jr.: Contraception **6:** 99, 1972.
4. Newton, J., Elias, J., and McEwan, J.: Lancet **2:** 951, 1972.
5. Shalia, N. G., Lane, M. E., and Sobrero, A. J.: Am. J. Obstet. Gynecol. **12:** 110, 1975.
6. Med. Lett. **12:** 26, 1975.
7. Hefnawi, F.: Contraception **9:** 133, 1974.
8. Mishell, D. R., Jr.: Fam. Plann. Perspect. **7:** 103, 1975.
9. Editorial: Obstet. Gynecol. Surv. **30:** 55, 1975.
10. Barranco, V. P.: Arch. Dermatol. **106:** 386, 1972.
11. Christian, C. D.: Am. J. Obstet. Gynecol. **119:** 441, 1974.
12. Tietze, C.: Studies in Family Planning, The Population Council, No. 18, 1967.
13. Ansari, A. H.: Obstet. Gynecol. **44:** 727, 1974.

Discussion

Dr. C. Stedman Glisson, Jr., Atlanta, Georgia. Drs. Nebel, Currie, and Lassiter have presented an excellently documented and timely paper on the Cu-7 IUD with excellent results.

I believe two key statements by them are: "Patients who selected this form were counselled regarding its effectiveness, limitations, and complications" and "We feel that these figures reflect proper patient selection and insertion timing, combined with meticulous insertion techniques". Their protocol and techniques were well thought out and these efforts were evident in the results so clearly outlined by them. IUD's are excellent, but not intended for use in everybody or by everybody.

I felt that discussion by one doctor or group would not be as effective as that of multiple doctors and offices. Therefore I surveyed 80 board-certified Ob.-Gyn. doctors in Atlanta—nine solo and 71 in groups of two to six doctors. The opinions and findings were as varied as expected.

The Cu-7 has been sold well to doctors and patients in Atlanta. Three doctors do not use it, 12 rarely use it, 32 use it predominantly, and 33 use it exclusively. Eleven of 20 groups use Cu-7 exclusively. Insertion is done only during menses by 76, whereas four inserted it at any time during the cycle.

Philosophy varied from lackadaisical approach to serious concern, using careful selectivity, including counselling plus literature given patients with advice to return later with decision for or against insertion. It was these doctors who had the best record, with fewer complications. Best results were in those patients with high motivation and willingness to accept the price of the side effects to insure contraceptive protection, when they could not take pills or had failure from other modalities.

Bleeding varied from 10 to 100 per cent during the first 1 or 2 months with no treatment other than removal of 4.05 per cent and an average of 15 per cent called serious. Of a total of 6,327 insertions, 60 were removed for infections (0.948 per cent), mostly occurring after many months, with 27 other early fevers. There were five perforations with three removals by laparotomies and two laparoscopic removals.

There were 49 pregnancies (0.77 rate). Of these, 20 went to term without abnormalities or complications of pregnancy. The remainder resulted in abortions upon removal of IUD, or had therapeutic abortion immediately, doctors and patients fearing abnormalities, etc. One pregnancy occurred in a double uterus with two Cu-7's inserted. Pain varied greatly, from 2 to 50 per cent, with 50 per cent being nulliparas in some series. Only 5.4 per cent Cu-7's were removed for pain alone.

A few comments from those with best results were: "Don't insert IUD in uterus with acute angulation, anterior or posterior"; "Don't insert nulliparas with less than 6 cm. depth of uterus"; "Communicate with patient regarding problems before insertion."

The newer inserter makes insertion better and easier and decreases one major complaint.

Removal in 2 years has been another factor which has received adverse comment from patients and doctors alike.

Also, the higher cost of the Cu-7 detracts.

At least half of the doctors use Cu-7 as a primary device in nulligravidas; the remainder stated that they do not use, or seldom use, a Cu-7 in nulligravidas because of difficulty in inserting without increased pain, bleeding, or rejection; they preferred the small Saf-T-Coil or Lippes loop.

The variety of findings and responses of the doctors relative to effectiveness and use of the Cu-7 makes one realize two things. (1) The Cu-7 is good but not the full answer, only another step up our ladder in the search for the perfect birth-control device. (2) We are reminded of the old adage that it's not the instrument used but the facility with which the instrument is used.

A composite vaginal vault suspension using fascia lata

JOHN H. RIDLEY, M.D.
Atlanta, Georgia

A description of a composite procedure is offered as a further effort to have a safe, relatively easy, and dependable surgical operation for complete vaginal prolapse in the sexually active woman. The fact is generally accepted that the combination vaginal and surgical approach done at the same sitting gives a better chance for cure where either single approach has proved to be less dependable. Nothing startling new is claimed, but the selection of the homologous fascia lata as the suspending material used technically in a simple, safe manner is outlined. Twelve patients have had this procedure done in the past 4 years with no recurrence of the prolapsed vault and no complaint of dyspareunia by either partner. One patient has had recurrent enterocele even though effort had been made to prevent this. There has been no death in this series. (AM. J. OBSTET. GYNECOL. 126: 590, 1976.)

COMPLETE PROLAPSE of the vaginal vault, vaginal inversion, or procidentia are practically synonymous and pose a challenge to the gynecologic surgeon. No one surgical procedure has yet been fully accepted as satisfactory enough to exclude all others. The likelihood of the prolapse is made apparent by many unrelated factors etiologically, i.e., the number and difficulty of vaginal deliveries, physical activity of the patient, and inherent strength or integrity of the affected tissues. These cases of complete vaginal prolapse may be primary, with no previous trauma whether obstetric or surgical, or they may be secondary failures of previous surgical efforts.

The indications for correction of this condition are multiple, both subjective and objective. The patient may find that the protruding vagina with or without the uterus is intolerable because of the discomfort of walking, sitting, straining to void or to defecate, and unsatisfactory coitus for both herself and her partner. Objectively, the gynecologist may find that the dependent bladder, as it is usually present, has a chronically infected residual urine leading to dysuria and ascending urinary tract infection with possible serious permanent damage to the upper urinary tract. There are nearly always present the enterocele and the rectocele leading to severe pelvic pressure, backache, and rectal impaction. Ulceration of the prolapse (exposed, vaginal mucosa) may occur and compound the problem. There may be found the rather rare but interesting "internal cystocele" as the bladder prolapses backward into the large enterocele.

The one most important factor in selecting a surgical effort is whether the patient will remain sexually active. If not, the complete colpocleisis or a modification thereof can be considered. In very carefully selected cases, this procedure of colpocleisis can solve a problem of prolapse and be eminently satisfactory for the patient.[1]

On the other hand, where the vaginal canal is to be preserved, the gynecologist must consider the conservative effort, such as the use of a satisfactory and removable pessary, or finally the surgical effort of suspending the vaginal vault and preserving a functional vagina. Much has been written about the dilemma of making the most suitable selection of the treatment for prolapse and whether it should be (1) conservative (pessary); (2) obliterative (colpocleisis); or (3) preservative (vaginal vault suspension).

Of the many surgical procedures that have been described to suspend and preserve the vagina, there have evolved three categories: (1) ventrofixation, now rarely done; (2) sacral colpopexy or hysteropexy, as the case may be; (3) anterior abdominal wall suspension of the vaginal vault. Review of the literature reveals that historically there have been no less than 43 well-documented descriptions of operations for this condition.[2–5] These have been described and performed by many competent surgeons, but only a relatively few are mentioned and recommended in the current gynecologic surgical textbooks.[6, 8] To enumerate these

Presented at the Thirty-eighth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hamilton, Bermuda, January 24-29, 1976.

Reprint requests: Dr. John H. Ridley, 35 Collier Road, N.W., Atlanta, Georgia 30309.

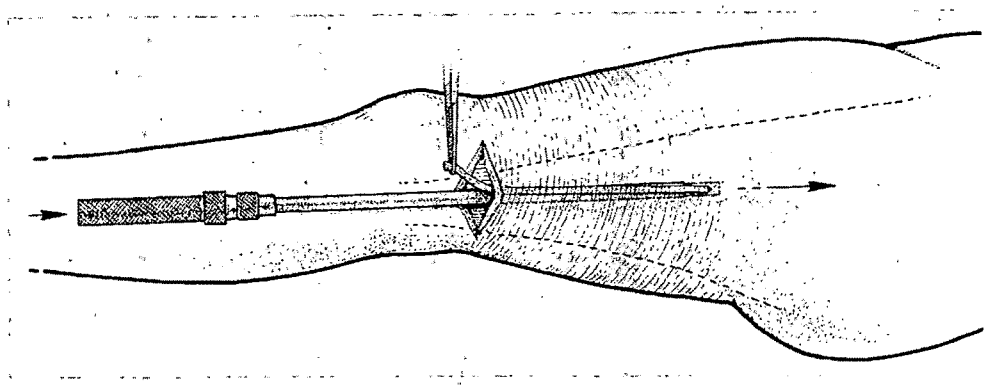


Fig. 1. Procurement of fascia lata strap with Masson stripper. The instrument is being thrust cephalad as high as possible with fascia strap passing through eye of instrument.

would not be permissible in the time and space allowed. Suffice it to say, a more efficient, dependable, and safe procedure is being sought and thus the present procedure is described.

Although a wide variety of materials have been used to aid in the vaginal vault suspension, it is well accepted that homologus tissues, i.e., fascia lata, are best tolerated by the host.[7, 8] Numerous operations have been described in which foreign organic materials (ox fascia, kangaroo tendon) and inorganic materials (stainless-steel staples and wire, Teflon, Merseline, etc.) have been utilized. There is an increased incidence of host rejection to these foreign materials, leading to postoperative complications and failures.

Materials and methods

The combined vaginal and abdominal approach, using straps of homologus fascia lata, has been used in a series of 12 cases, from 1971 through 1975, with very satisfactory results. All patients desired to be yet sexually active and were in good enough general physical condition to permit the surgical procedure. The ages of the patients varied from 49 to 72 at the time of surgery. All have been followed for at least 6 months or longer postoperatively. Colporrhapgy and perineorrhaphy were consistently needed in this group of patients. Ten of the 12 had enterocele of varying degree. All continued to be sexually active postoperatively. On direct questioning, none complained of dyspareunia on the part of herself or her sexual partner postoperatively.

Technique

Under general anesthesia, the patient is first placed in the supine position with the lower thigh exposed laterally and to the middle aspect of the knee joint. A strap of fascia lata is taken through a small 5 to 6 cm. incision made one finger-breadth cephalad to the level

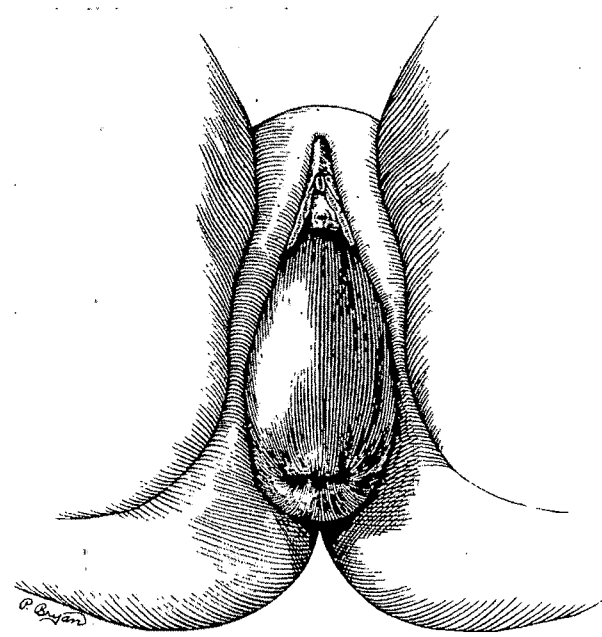


Fig. 2. Complete vaginal and uterine prolapse in 54-year-old sexually active patient.

of the superior aspect of the patella and directly over the iliotibial band. Even in the aged person this structure is easily identifiable just above its insertion into the lateral condyle of the femur. The Masson stripper is used (Fig. 1) to quickly procure this ribbon of tissue and with very little or no difficulty. The technique of obtaining this fascia lata strap is described in detail elsewhere in the literature.[8]

The patient's position is changed to lithotomy and routine vaginal and perineal preparation is done. The presenting prolapse is evaluated as well as possible, considering whether the uterus and cervix remain and whether there is any evidence of any other pelvic pathology (Fig. 2).

The uterus, if present, is best removed at this time.

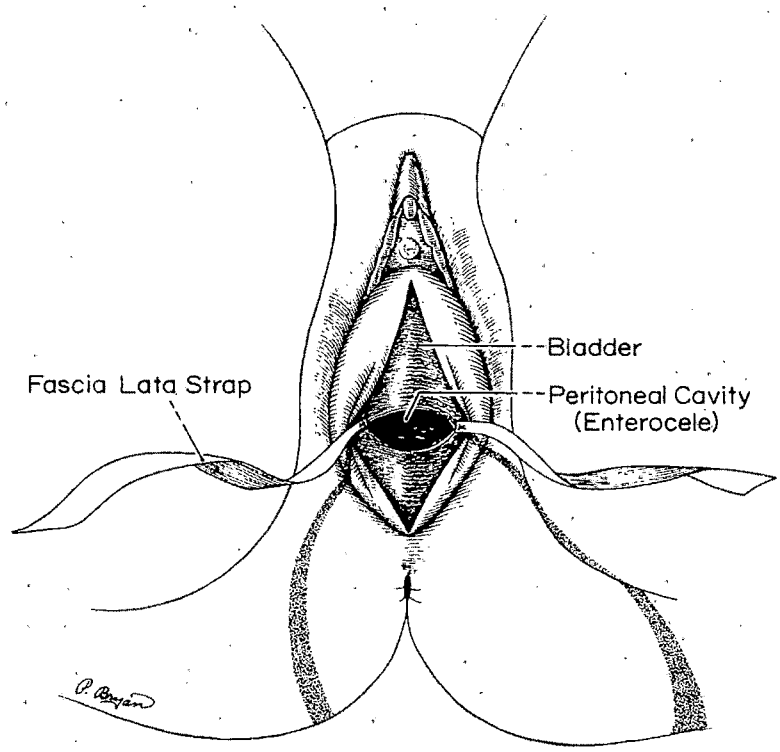


Fig. 3. Each end of a band of the fascia lata strap has been sutured securely at the right and left vaginal fornix or seam, respectively, to the vaginal mucosa and remnants of the bases of the broad ligaments and uterosacral ligaments. The free ends of the fascia lata straps are ducked into the pelvic cavity after the enterocele sac has been explored and extirpated, and just before closure of this peritoneal opening.

The vaginal hysterectomy performed under these circumstances is usually quickly performed and enterocele evaluated. This is to be obliterated, as will be described more fully. The operator will estimate the amount of redundant vaginal mucosa to be removed and yet conserve enough to rebuild an adequate and functional vagina. The subjacent vaginal fascia or connective tissue is developed by a routine dissection from the overlying vaginal mucosa and well plicated in the midline with chromic 0 catgut as is done in an ordinary colporrhaphy. It has been our routine to perform a Kelly plication of the paraurethral tissues prophylactically even though the patient has not complained of stress urinary incontinence previously. It is a recognized fact that stress urinary incontinence may result from or be re-established in the course of the operation for procidentia. Posterior colporrhaphy and perineorrhaphy are then routinely done.

Particular attention is to be paid to the recognition and obliteration of the enterocele which is practically always present without exception in these cases of vaginal inversion. The enterocele sac is opened directly and explored.

Before the neck of the enterocele sac is obliterated, thus closing the peritoneal cavity, one end of each of the fascia lata bands (the original length of fascia lata band has been divided crosswise into two equal lengths) is sutured securely with 2-0 silk to a point in the right and left fornix of the vaginal vault, respectively. The point for this vaginal attachment is selected carefully at the lateral aspect of either side of the vaginal vault seam, if the uterus had been previously removed. In those cases where vaginal hysterectomy is being performed in conjunction with this suspension and repair, the end of the fascia lata band is secured in the vaginal fornix, incorporating the vaginal mucosa, the pedicles of the base of the broad ligament, and uterosacral ligament. The suture fixation of these ends of fascia lata is done under direct vision, greatly decreasing the hazard of injury to the ureters, base of the bladder, or the pelvic vessels. The loose ends of the fascia lata bands are now tucked into the opening in the cul-de-sac where the enterocele has been opened and its sac entirpated prior to its closure (Fig. 3). The closure of the peritoneal opening is now done with a purse-string suture as high as safely possible at this stage of the

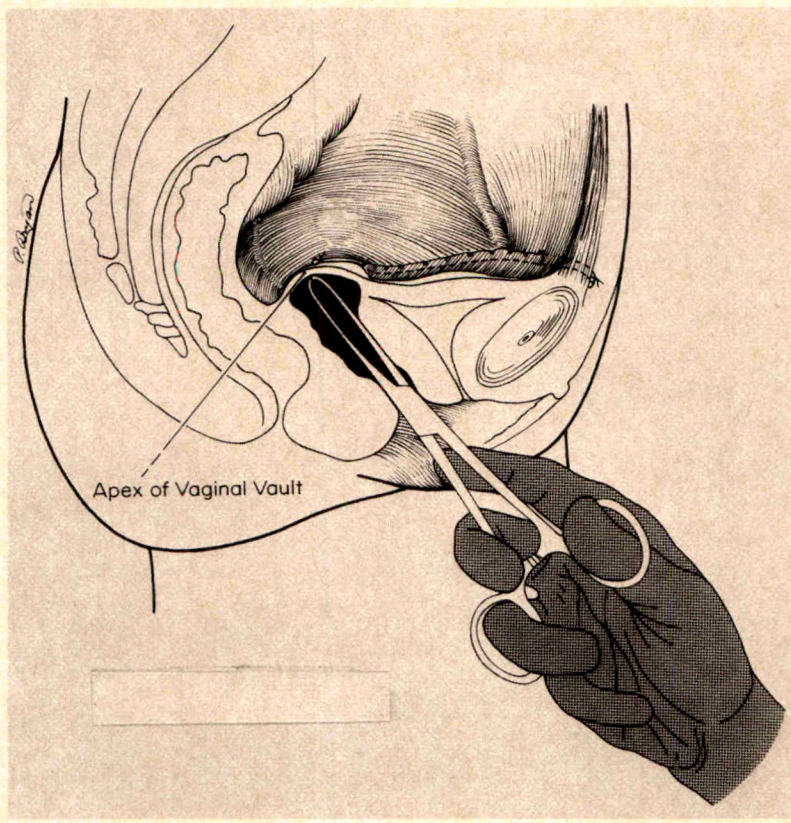


Fig. 4. In a case in which the peritoneal cavity (enterocele) cannot be entered, each lateral vaginal fornix is grasped with a long Allis clamp for upward thrust during abdominal phase of the operation. This accurately identifies the exact location for attachment of the fascia lata straps from above.

procedure. Now the overlying connective tissue, remnants of the ureterosacral ligaments, and fascia are plicated with chromic 0 catgut. The remainder of the vaginal repair is completed per routine with condensation and plication of as much of the subjacent vaginal fascia as possible. The perineorrhaphy is done per routine to complete this stage of the procedure.

In the event that the enterocele sac is not present or is not found, the extensive vaginal repair is completed per routine and the fornices of the vagina are clamped with long Allis clamps for identification by the upward thrust of an assistant during the abdominal phase of the procedure (Fig. 4). In one case, the rectum was accidentally opened in the vaginal search for the enterocele. The defect was recognized and closed in three layers with double 00 chromic catgut. Since this rectal entry had been extraperitoneal, no difficulty was anticipated and, as was the case, none was encountered. The operation was completed per routine.

The patient is now placed again in the supine position and the lower abdomen entered through a lower midline incision. The free ends of the inverted fascia lata straps are easily identified in the cul-de-sac. Each free end is led through a tunnel in the vicinity of internal inguinal ring as may be done with the round ligament in the suspension of the uterus. A long Kelly clamp is passed between the anterior abdominal aponeurosis and the belly of the rectus muscle. The point is presented at the preselected area near the internal inguinal ring, with care not to injure the inferior epigastric vessels. The free ends of each fascia lata strap are grasped and drawn upward and then medially to be fixed without undue tension to the under surface of the anterior abdominal aponeurosis with 2-0 silk approximately 2 cm. to either side of the midline (Fig. 5). The exposed portion of the fascia lata band intra-abdominally is then enshrouded or enfolded into the folds of the parietal peritoneal, with a continuous suture of double 0 chromic catgut, being careful not to injure any subjacent structures. Thus the fascial bands are safely extraperitonized and give no chance for an intra-abdominal strangulation of any tissue slipping through an orifice.

As a final step in the procedure, a Moschowitz procedure is done to obliterate the cul-de-sac with progressive purse-string sutures from the depth of the

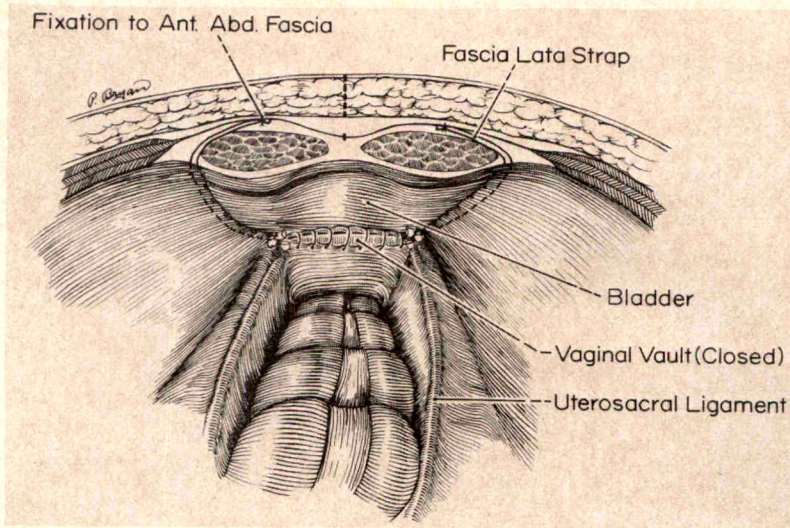


Fig. 5. Intra-abdominal view of attachment of fascia lata straps from vaginal vault to under surface of the anterior abdominal aponeunosis. The cul-de-sac will now be obliterated by the Moschowitz procedure up to level of vaginal vault apex, plicating the uterosacral ligaments in the midline. The filling bladder will not be deformed by the presence of any midline suspension.

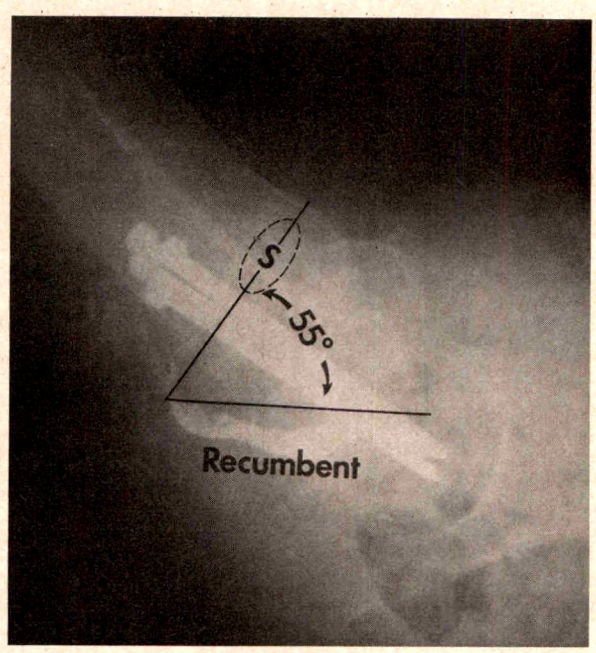


Fig. 6. Postoperative lateral colpogram showing relationship of the suspended vagina to axis of the symphysis pubis (2 years postoperative).

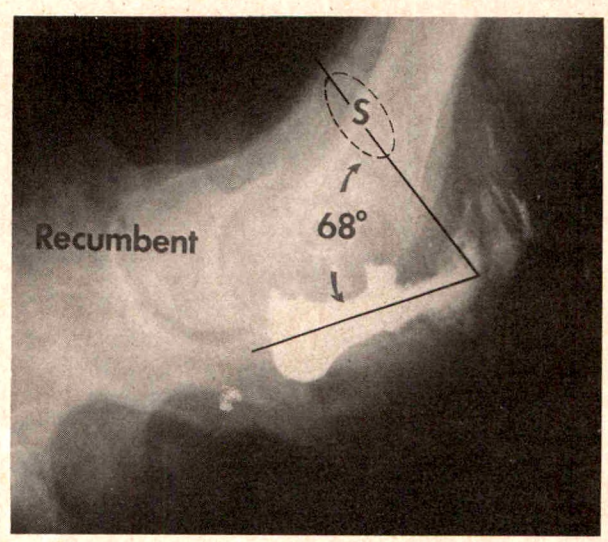


Fig. 7. Postoperative lateral colpogram showing adequate vaginal depth and caliber. None of these patients voiced any complaint of dyspareunia by herself or her partner (10 months postoperative).

cul-de-sac to the apex of the suspended vagina.[9] Thus the so-called pelvic plate is strengthened, practically obviating the chance for postoperative recurrence of the enterocele.

In the event that the operator has not been able to enter the peritoneal cavity vaginally to fix and invert the fascia lata bands, the tips of the long Allis clamps in either fornix of the vaginal vault are identified as an assistant thrusts these clamps upward (Fig. 4). By careful dissection, avoiding injury to the adjacent urinary tract and pelvic vessels, the vaginal vault mucosa is identified and the fascia lata bands are attached to the left and right aspect of the vaginal apex, respectively. The suspension of the vaginal vault is then carried out as described above. Because of the possibility of urinary tract injury in this type of case, where the identification of the vaginal vault must be done from

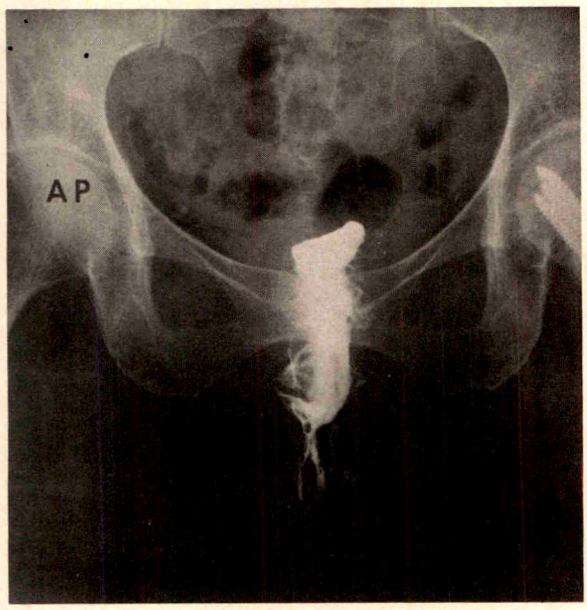


Fig. 8. Two year postoperative A-P colpogram showing vagina without apex contracture and with adequate depth and caliber.

above, ureteral catheters might be placed preoperatively for safe identification of these structures which can be altered in position and fixed by previous surgical scarring.

Results

The over-all results in this series of cases have been satisfactory both in the immediate postoperative period and in the longer term follow-up. There has been no death. Two cases showed a morbidity beginning on the third and fourth postoperative days, respectively, due to an acute flareup of urinary tract infection. Each was controlled with appropriate therapy. The average postoperative hospital stay was 7 days.

It is thought that a year is long enough to evaluate the results as to the degree of success or failure in these cases. There have been no recurrences of the vault proplapse and the vaginal depth has remained satisfactory. One enterocele had recurred even though care had been exercised to reinforce the pelvic musculofascial plate. To date, this particular patient has not expressed any desire to have any further repair performed.

There have been no complaints of dyspareunia by either partner and this must be considered a most important fact in follow-up. Postoperative colpograms reveal the angle of inclination of the suspended vagina to be between 55° and 68° from the axis of the symphysis pubis (Figs. 6 and 7). The anteroposterior colpogram shows a vagina of adequate depth and without any conical deformity of the apex (Fig. 8). Lateral cystograms showed no deformity of the filled (350 c.c.) bladder. One patient continued to have a moderate stress urinary incontinence which was not successfully corrected by the Kelly type plication of the vesical sphincter during the procedure. She has declined any further attempt at correction of this thus far.

Summary and conclusions

A composite operation has been presented in which various modifications of the use of suspending material, technical steps, and safeguards against injury and recurrence are described. No effort is made to take away from any of the numerous other good procedures that have been described previously, but the chief purpose of this procedure, as presented, is an effort to take a step forward in perfecting a safe and dependable procedure for correction of the difficult problem of vaginal prolapse. Since neither the vaginal repair alone nor an abdominal suspension alone will dependably correct the vaginal prolapse, the combination of a vaginoabdominal approach is well recognized as the best surgical plan. Possibly too much attention has been paid to the angle of inclination of the vaginal vault because there seems to be no perfect answer. In final analysis, it is accepted that a comfortably functional vaginal canal is what it is all about.

REFERENCES

1. Ridley, J. H.: Evaluation of the colpocleisis operation: A report of 58 cases, Am. J. Obstet. Gynecol. **113:** 1114, 1972.
2. Ward, G. E.: Ox fascia lata for reconstruction of round ligaments in correcting prolapse of vagina, Arch. Surg. **36:** 163, 1938.
3. Falk, H. C.: Uterine prolapse and prolapse of the vaginal vault treated by sacropexy, Obstet. Gynecol. **18:** 113, 61.
4. Randall, C. L., and Nichols, D. H.: Surgical treatment for vaginal inversion, Obstet. Gynecol. **38:** 327, 71.
5. Birnbaum, S. J.: Rational therapy for the prolapsed vagina, Am. J. Obstet. Gynecol. **115:** 411, 73.
6. TeLinde, R. W., and Mattingly, R. F.: Textbook of Operative Gynecology, ed. 4, Philadelphia, 1970, J. B. Lippincott Company, Chap. 24.
7. Beecham, C. T., and Beecham, J. B.: Correction of prolapsed vagina or enterocele with fascia lata, Obstet. Gynecol. **42:** 542, 73.
8. Ridley, J. H., et al.: Textbook of Gynecologic Surgery: Errors, Safeguards and Salvage, Baltimore, 1974, The Williams & Wilkins Company, Chap. 4.
9. Moschowitz, A. V.: The pathogenesis, anatomy, and cure of prolapse of the rectum, Surg. Gynecol. Obstet. **15:** 7, 1942.

Discussion

Dr. Coy L. Lay, Lakeland, Florida. Dr. Ridley is known not only for his extensive experience in pelvic surgery but also for his ability to teach and describe his techniques. His recent book *Gynecologic Surgery—Errors and Safeguards* is stimulating to our residents, but it is even more challenging to the experienced pelvic surgeon. Likewise, Dr. Ridley in this paper described his operation well, and this operation will be a challenge to the experienced pelvic surgeon in his attempts to correct a most difficult problem in a highly select group of patients.

Dr. Ridley himself has written that no claim is being made for anything startlingly new in this operation, but it is an accumulation of ideas and variations of techniques which he has found practical for patients with procidentia when preservation of vaginal function is important.

A simplified outline of Dr. Ridley's composite operation can be summarized as follows: (1) A strip of fascia lata should be removed. (2) anterior and posterior pelvic repair should be followed by removal of the uterus if it is still present. Strips of fascia lata should be sutured to the upper vagina, with the ends pushed inside the peritoneal cavity before vaginal closure. (3) Laparotomy should be performed with fixation of strips of fascia lata to the pelvic wall and underside of the rectus muscle. Moschcowitz's purse-string sutures applied to obliterate the cul-de-sac.

It would be remiss at this point if we did not recognize the similarity of the procedure Dr. Ridley has presented to the Williams-Richardson operation, proposed in 1952 by the current President-elect of this Society, Dr. Cullen Richardson. Drs. Williams and Richardson reported the use of fascia from the abdominal wall in a paper presented to this Society exactly 24 years ago this month.

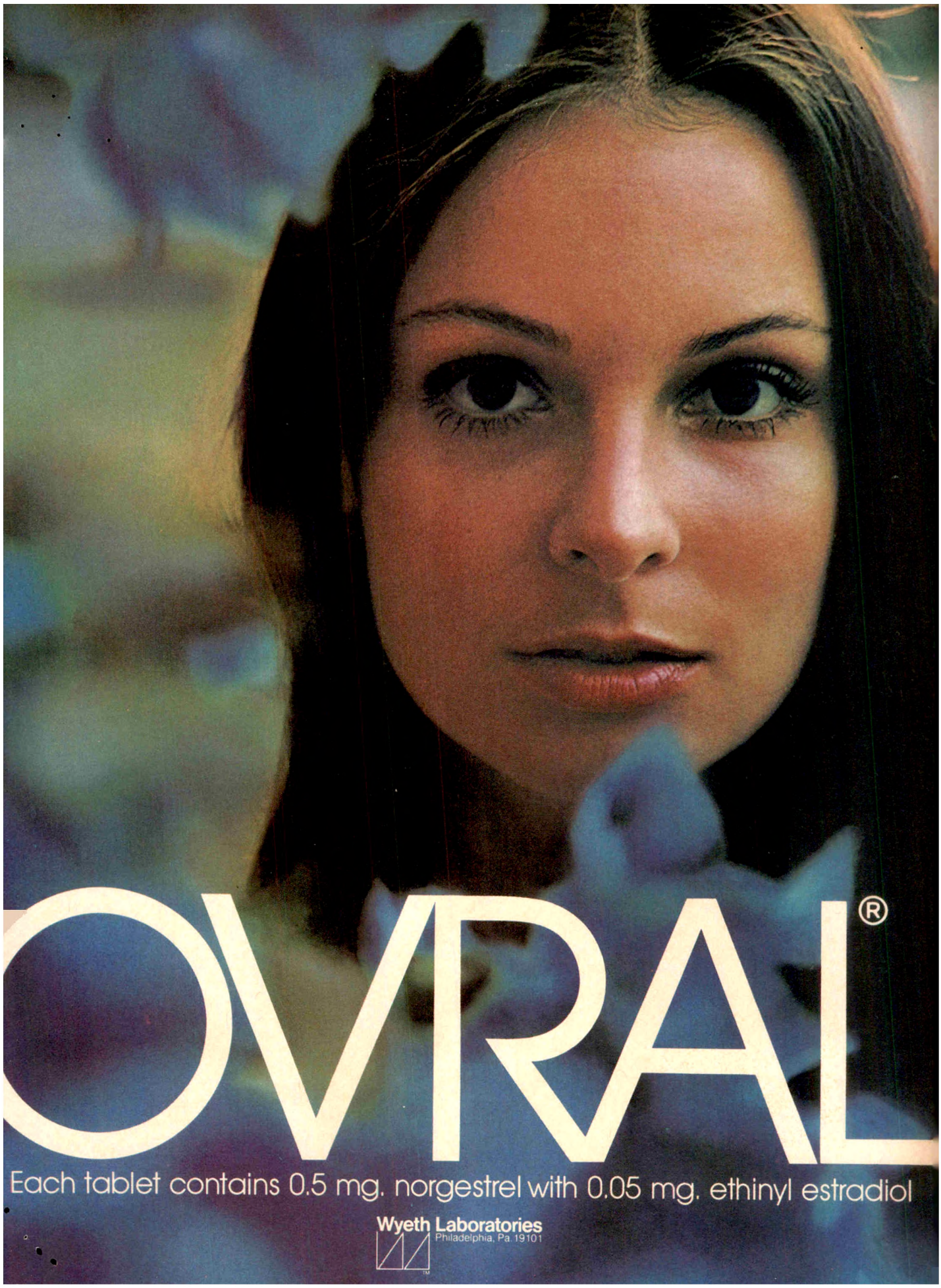
Since then, the use of fascia from the rectus muscle has been more widely utilized in the southern part of the country. In 1969, Dr. Richardson presented his second report on this subject to the South Atlantic Association in a paper giving the long-term results of utilizing abdominal fascia.

Although satisfactory fascia for additional vaginal support can sometimes be obtained from either fascia lata or from the rectus muscle, the fascia lata seems to be consistently stronger, especially when previous abdominal operations have left scars on the rectus fascia.

There are certain dangers inherent in this operation which warrant special care in technique. When the fascia is being sutured to the upper corners of the vagina from below, the ureters will be in close proximity and must be carefully identified. Of course, in the abdominal portion of the operation, the fascia is again sutured in close proximity to the ureter and the Moschcowitz purse-string sutures of the cul-de-sac can incorporate a ureter if improperly applied. However, careful attention to suture placement should prevent ureteral damage.

The operation may seem quite complex, but the problem of recurrent procidentia can also be quite complex and difficult to manage, especially in the very elderly. One may only need recall the elderly patients in nursing homes for whom innumerable vaginal pessaries of various sizes, shapes. and materials have been devised. Few are satisfactory. For this type of patient, we have even tried "instant tissue glue" to perform a modified LaForte type of operation without anesthesia. Only limited success is being achieved with this "instant glue technique." If these unfortunate patients had been treated more aggressively, as advocated by Dr. Ridley, when they were younger and could better tolerate extensive operation, possibly these less satisfactory supports would not be necessary in later years.

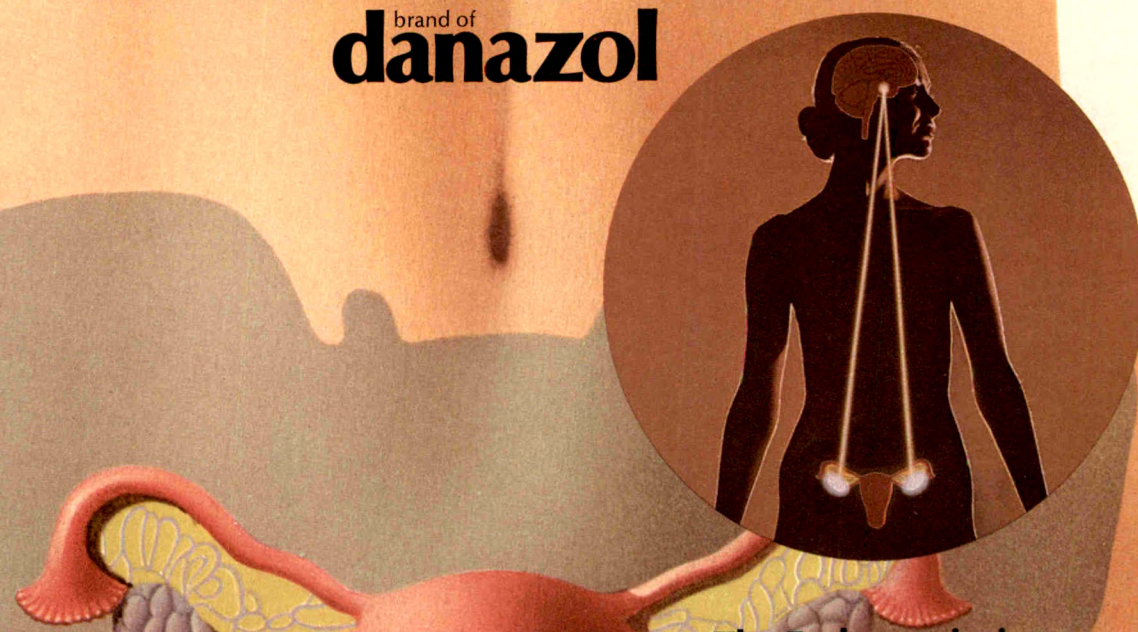
In summary, Dr. Ridley should be complimented on presenting a practical and useful clinical paper. He has summarized his surgical experiences with a difficult clinical problem and has emphasized the use of fascia lata to make an old procedure a step better.


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol
Wyeth Laboratories
Philadelphia, Pa. 19101

Winthrop Laboratories announces a new gonadotropin inhibitor

Danocrine®

brand of
danazol



The Endometriosis Signs and Symptoms Profile

Dysmenorrhea

Pelvic Pain

Dyspareunia

Induration of the cul-de-sac

Infertility

Now–a pharmacologic agent specifically for endometriosis

- proven both effective and well accepted
- in selected cases, an alternative to surgery and to existing hormonal therapy*

After Treatment with Danocrine® In 267 patients†

Complete or partial relief in 96% of 227 patients with this symptom	Endometriosis can be characterized by any of these signs and symptoms. After initiation of therapy, effectiveness was measured by relief of dysmenorrhea, pelvic pain, dyspareunia and decreasing induration of the cul-de-sac. (See adjoining table for clinical data to date on symptomatic relief with new Danocrine.)
Complete or partial relief in 89% of 226 patients with this symptom	
Complete or partial relief in 84% of 115 patients with this symptom	
Complete or partial relief in 82% of 185 patients with this sign	
Preliminary evidence suggests significant benefit in cases of infertility associated as a symptom of endometriosis††	

New Danocrine® brand of danazol usually offers dramatic relief from the symptomology caused by endometriosis

*See important prescribing information, including warnings, precautions, adverse reactions, patient selection, and dosage recommendations on last page.

†Data on file, Winthrop Laboratories.

Danocrine is indicated in those patients:

- who cannot tolerate other drugs.
- in whom other effective drugs are contraindicated.
- who fail to respond to adequate doses of other effective drugs.
- in whom surgery alone is considered not to be the treatment of choice.

Well-accepted

- Generally mild side effects profile—avoids the potentially serious hormonal effects of conventional high dosage estrogenic and progestational regimens.
- Non-estrogenic and non-progestational.
- No stimulating effect upon ectopic endometrial tissue.

Generally reversible antigonadotropic action

Generally, on completion of therapy, the antigonadotropic activity of Danocrine is reversed, resulting in a return of ovulation and cyclic menstrual bleeding within 60-90 days.

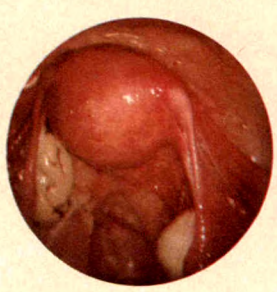
High degree of clinical success confirmed by laparoscopic photographs

Clinical trials with new Danocrine have indicated an efficacy and tolerability previously unattainable through pharmacological therapy. And therapy with Danocrine has the capability of resolving microscopic foci not amenable to surgical removal. In clinical trials to date,* complete or partial resolution of symptoms has been reported in 82-96% of 267 patients. In certain cases, these findings have been confirmed visually by laparoscopy and biopsy[1] (see photos).

Severe bilateral ovarian endometriomas



After 221 days of Danocrine therapy



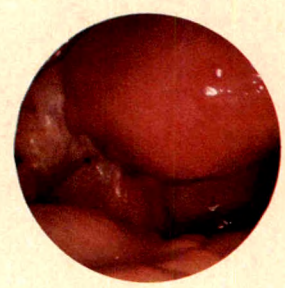
Moderate unilateral ovarian endometrioma



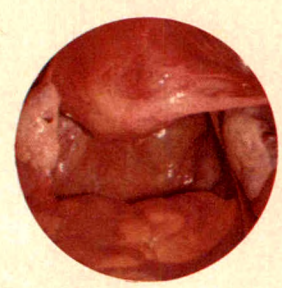
After 189 days of Danocrine therapy



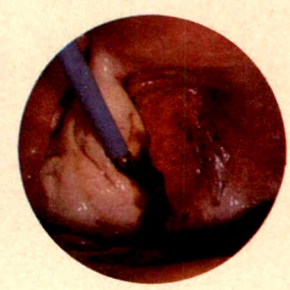
Left adnexal endometrioma



After 196 days of Danocrine therapy



Moderate pelvic endometriosis



After 227 days of Danocrine therapy



New Danocrine®

brand of

danazol

Now—a pharmacologic agent specifically for endometriosis

*Data on file, Winthrop Laboratories.

1. Dmowski, W.P. and Cohen, M.R.: Treatment of endometriosis with an antigonadotropin, Danazol: a laparoscopic and histologic evaluation, *Obstet. Gynecol.* 46:147, Aug. 1975.

See important prescribing information, including warnings, precautions,

Danocrine®
Brand of danazol

Indications: Until additional studies have been completed which define the lowest clinically effective dose, Danocrine is indicated for the treatment of endometriosis amenable to hormonal management and only for those patients 1) who cannot tolerate other drug therapy, 2) in whom other effective drugs are contraindicated, or 3) who fail to respond to other effective drug therapy when given in adequate doses.

Danocrine is not indicated in those patients where surgery alone is considered the treatment of choice.

Contraindications: Danocrine should not be administered to patients with:

1. Undiagnosed abnormal genital bleeding.
2. Markedly impaired hepatic, renal, or cardiac function.
3. Pregnancy.
4. Breast feeding.

Warnings: Further studies are ongoing to define the lowest clinically effective dose of Danocrine. Consequently, at the present time, Danocrine should be limited in its use to the select group of patients mentioned in the *INDICATIONS* Section. In view of the fact that some cases of endometriosis may be resistant to one specific form of hormone therapy and responsive to another, Danocrine may prove to be of benefit in such cases. There are some limited data in support of the use of Danocrine in therapy-resistant cases of this type.

While no embryotoxic or teratogenic effects attributable to administration of Danocrine have been observed in reproduction studies in animals, safe use of the drug in pregnancy has not been established clinically. If a patient becomes pregnant during treatment, administration of the drug should be discontinued.

Patients should be watched closely for signs of virilization. Some androgenic effects may not be reversible even when drug administration is stopped.

Precautions: Because Danocrine may cause some degree of fluid retention, conditions that might be influenced by this factor, such as epilepsy, migraine, or cardiac or renal dysfunction, require careful observation.

Adverse Reactions: The following androgenic effects have occurred in patients receiving Danocrine: acne, edema, mild hirsutism, decrease in breast size, deepening of the voice, oiliness of the skin or hair, and weight gain.

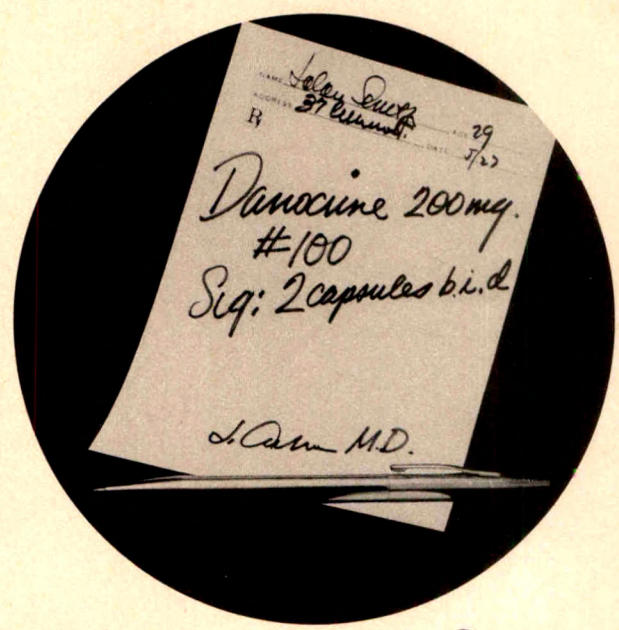
Also hypoestrogenic manifestations such as flushing, sweating, vaginitis including itching, dryness, burning and vaginal bleeding, nervousness, and emotional lability have been reported.

Although the following reactions have also been reported, a causal relationship to the administration of Danocrine has neither been confirmed nor refuted: *allergic*: skin rashes and rarely, nasal congestion; *CNS effects*: dizziness, headache, sleep disorders, fatigue, tremor, and rarely, paresthesia in extremities, visual disturbances, changes in appetite, and chills; *gastrointestinal*: gastroenteritis, and rarely, nausea, vomiting, and constipation; *musculoskeletal*: muscle cramps or spasms, and pain in back, neck, or legs; *genitourinary*: rarely, hematuria; *other*: loss of hair, changes in libido, elevation in blood pressure, and rarely, pelvic pain.

Dosage and Administration: The dosage of Danocrine is 800 mg., divided into two doses per day, until additional studies on the effectiveness of lower doses are completed. Therapy should continue uninterrupted for 3 to 6 months but may be extended to 9 months if necessary. After termination of therapy, if symptoms recur, treatment can be reinstituted.

How Supplied: Capsules of 200 mg. (orange), bottles of 100.

Winthrop Winthrop Laboratories, New York, N.Y. 10016
(1680M)



New Danocrine®
brand of
danazol
Now–a pharmacologic agent specifically for endometriosis

Ortho-Novum 1/50 TRADEMARK □21 and 28

Each yellow tablet contains 1 mg norethindrone and 0.05 mg mestranol.
Each green tablet in the 28-day regimen contains inert ingredients.



©Ortho Pharmaceutical Corporation, 1976
OJ 272-6

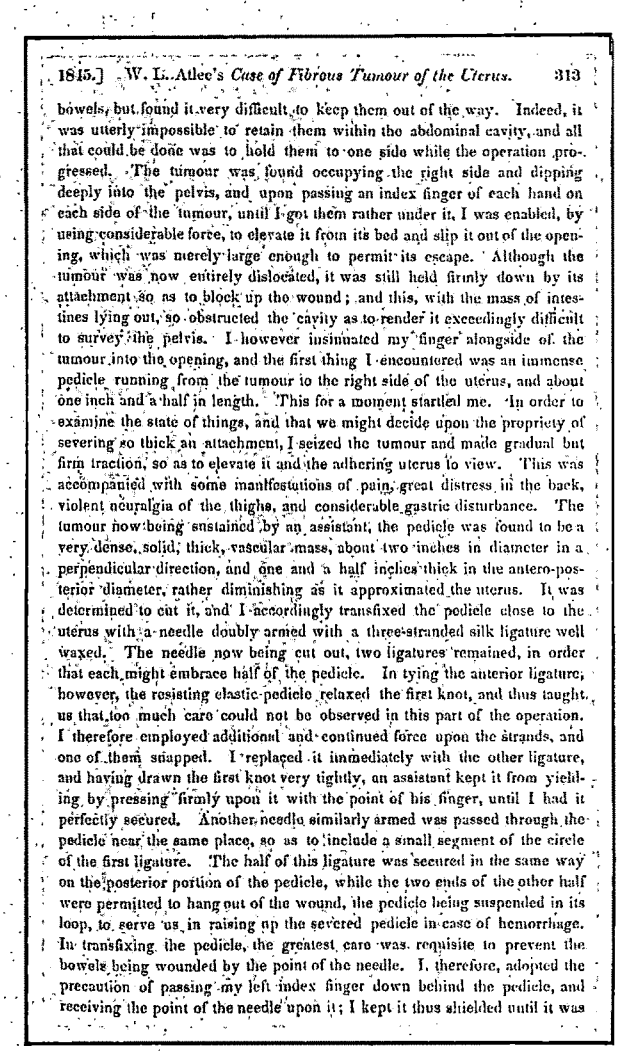
Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Case of a successful extirpation of a fibrous tumor of the peritoneal surface of the uterus by the large peritoneal section

WASHINGTON LEMUEL ATLEE

American Journal of the Medical Sciences, new series, vol. 9, pp. 309-335, 1845

Apparently, the first successful myomectomy was performed in 1844, by Washington L. Atlee of Pennsylvania. The patient, who was 24 years of age, had noticed a gradually enlarging tumor in the right lower abdomen for about one year. Atlee, with his brother John assisting, operated through an eight-inch midline incision. His preoperative diagnosis was an ovarian tumor rather than a uterine growth. Atlee recorded, "As soon as an opening was made into the peritoneum, most of the small intestines, several inches of transverse colon and a portion of the omemtum gushed out, and gave us a great deal of trouble during all the subsequent stages of the operation . . . my brother took charge of the . . ." (continued in the illustration). The neoplasm proved to be a pedunculated leiomyoma that weighed 1 pound, 13 ounces, and was about 18 inches in circumference. Despite a somewhat stormy postoperative course, the patient recovered to return home on the twenty-eighth postoperative day. A few years later, Atlee published the results of 14 further cases from his own practice (Trans. Am. Med. Assoc. 6: 545, 1853). In that paper, Atlee classified uterine leiomyoma according to the point of origin: extrauterine or surface tumors, intrauterine or cavity tumors, and intramural tumors. He was also one of the first to note that these lesions might undergo malignant degeneration. His surgical approach in these later cases was a combination of transcervical morcellation and enucleation of the leiomyoma by a long-handled bistoury or knife. At repeated operations, he sectioned into the substance of the tumor, scouping out portions. As might be expected, five of the patients died from peritonitis, septicemia, blood loss, and related complications. Despite these poor results, the paper received the annual prize essay award of the American Medical Association, because it dealt with tumors which had not previously been approachable surgically.



1845.] W. L. Atlee's *Case of Fibrous Tumour of the Uterus.* 313

bowels, but found it very difficult to keep them out of the way. Indeed, it was utterly impossible to retain them within the abdominal cavity, and all that could be done was to hold them to one side while the operation progressed. The tumour was found occupying the right side and dipping deeply into the pelvis, and upon passing an index finger of each hand on each side of the tumour, until I got them rather under it, I was enabled, by using considerable force, to elevate it from its bed and slip it out of the opening, which was merely large enough to permit its escape. Although the tumour was now entirely dislocated, it was still held firmly down by its attachment so as to block up the wound; and this, with the mass of intestines lying out, so obstructed the cavity as to render it exceedingly difficult to survey the pelvis. I however insinuated my finger alongside of the tumour into the opening, and the first thing I encountered was an immense pedicle running from the tumour to the right side of the uterus, and about one inch and a half in length. This for a moment startled me. In order to examine the state of things, and that we might decide upon the propriety of severing so thick an attachment, I seized the tumour and made gradual but firm traction, so as to elevate it and the adhering uterus to view. This was accompanied with some manifestations of pain, great distress in the back, violent neuralgia of the thighs, and considerable gastric disturbance. The tumour now being sustained by an assistant, the pedicle was found to be a very dense, solid, thick, vascular mass, about two inches in diameter in a perpendicular direction, and one and a half inches thick in the antero-posterior diameter, rather diminishing as it approximated the uterus. It was determined to cut it, and I accordingly transfixed the pedicle close to the uterus with a needle doubly armed with a three-stranded silk ligature well waxed. The needle now being cut out, two ligatures remained, in order that each might embrace half of the pedicle. In tying the anterior ligature, however, the resisting elastic pedicle relaxed the first knot, and thus taught us that too much care could not be observed in this part of the operation. I therefore employed additional and continued force upon the strands, and one of them snapped. I replaced it immediately with the other ligature, and having drawn the first knot very tightly, an assistant kept it from yielding by pressing firmly upon it with the point of his finger, until I had it perfectly secured. Another needle similarly armed was passed through the pedicle near the same place, so as to include a small segment of the circle of the first ligature. The half of this ligature was secured in the same way on the posterior portion of the pedicle, while the two ends of the other half were permitted to hang out of the wound, the pedicle being suspended in its loop, to serve us in raising up the severed pedicle in case of hemorrhage. In transfixing the pedicle, the greatest care was requisite to prevent the bowels being wounded by the point of the needle. I, therefore, adopted the precaution of passing my left index finger down behind the pedicle, and receiving the point of the needle upon it; I kept it thus shielded until it was

CURRENT DEVELOPMENTS

The critical control of progesterone levels and pregnancy by antiprogesterone

A. I. CSAPO*

T. ERDOS

St. Louis, Missouri, and Gif-sun-Yvette, France

Circulating plasma progesterone (P) has been quantitatively controlled in the rat "model" through highly specific binding by treatment with anti-P (A-P). Knowing the constant, which characterizes the binding of P to A-P in plasma, sequential assays of circulating A-P and A-P bound total P (Pt) revealed the levels of the biologically active unbound P (Pu). The studies showed that at different stages of gestation the mechanisms through which A-P reduces Pu and terminates pregnancy are the same. However, the doses of AP which effectively reduce Pu and also the critical levels of Pu at which pregnancy terminates are different. The moderate and transient physiologic P-withdrawal (Pw) at midterm permits the continuation of normal gestation, but pregnancy is terminated by a drastic and sustained reduction in Pu. In contrast, when Pu is only slightly and briefly reduced below physiologic levels, pregnancy continues and only retarded conceptus growth signals that Pw occurred. Apparently Pw has to be controlled and measured with "razor's-edge" precision to fully expose and define the regulatory significance of this steroid in the maintenance and termination of pregnancy. Short of this precision, the key regulator of the pregnant uterus will remain buried, as it has been during 40 years, in controversial findings. (AM. J. OBSTET. GYNECOL. 126: 598, 1976.)

THE CONTENTION of the pioneers[1] that the indispensability of progesterone (P) in pregnancy maintenance is a biologic law of broad validity during 40 years received only isolated support, based on physiologic rather than steroid chemical data.[2] However, reliable P assays revealed recently that normal pregnancy maintenance in animals and human patients cannot withstand the reduction of P levels to a *critical* value.[3]

This information can be expected to promote conceptual and clinical developments, when it is clearly understood that P withdrawal (Pw) is a qualitative expression and only Pw to a *critical* value has precise biologic meaning. This recognition is mandatory since the critical P value at which pregnancy terminates is *different* in the various species—indeed, even at different stages of gestation in the same species.[2, 3] Therefore, therapeutic attempts to control the endogenous regulatory mechanism of the pregnant uterus, including P, must achieve a "razor's-edge" precision in order to be predictably effective. The intent of this study is to examine the reality of this premise through the continued exploration of Corner's legacy.

The elegant immunologic technique[4] of binding

From the Department of Obstetrics and Gynecology, Washington University School of Medicine, and the Laboratoire d'Enzymologie C.N.R.S.

This study was supported by The Agency for International Development, Department of State, Contract No. AID/csd 3160.

Reprint requests: Arpad I. Csapo, M.D., Professor of Obstetrics and Gynecology, School of Medicine, Washington University, 4911 Barnes Hospital Plaza, St. Louis, Missouri 63110.

**Research Career Awardee of the CPR, NICHD, No. 5-K6-HD-20, 169.*

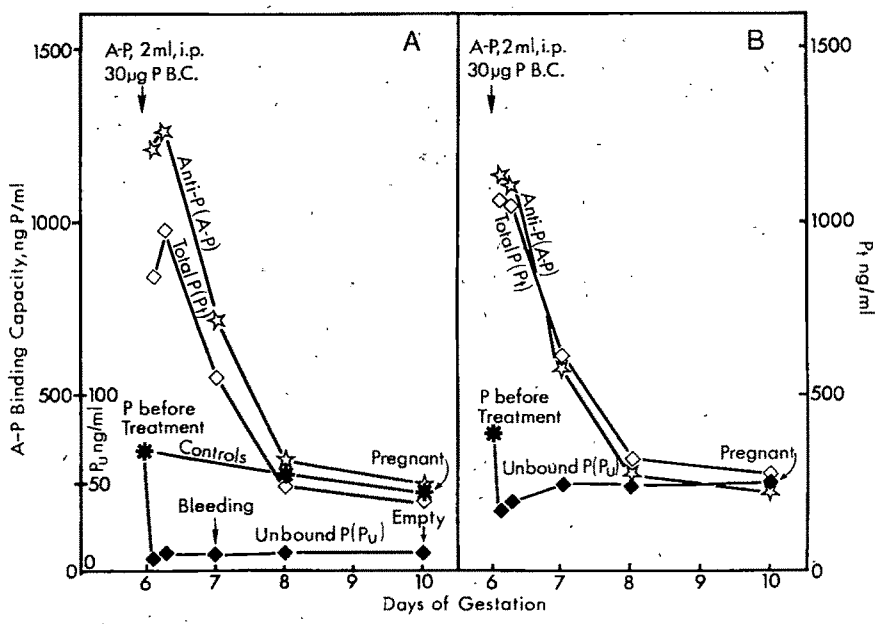


Fig. 1. The relationship between the degree of progesterone withdrawal and the maintenance of pregnancy in the rat "model." *A*, In the control rats the moderate P-withdrawal *(Pw)*, which normally occurs between days 6 and 10 of gestation, had no effect on pregnancy. In contrast, at day 6 of gestation an A-P dose, of 30 μg P BC, excessively bound P and sharply reduced the biologically active Pu to the abortion value. *B*, An intermediate is shown, between the two extreme conditions of normal and interrupted pregnancies, which developed when A-P only transiently reduced Pu below the physiologic level. Pregnancy continued, but the conceptuses had retarded growth. For detailed description, see text.

plasma P with the highly specific anti-P (A-P) permitted precise control over P levels in the rat "model." Sequential assays, following A-P treatment, of circulating A-P, total P (Pt), and unbound P (Pu) exposed[5] the precise quantitative relationship between A-P and Pu on the one hand and between Pu and pregnancy maintenance on the other. By quantitating the biologically active P fraction Pu, these assays also revealed that while at different stages of gestation the mechanisms of the maintenance and termination of pregnancy are the same, the endogenous P levels and the critical Pu at which pregnancy terminates are different. Therefore, the "binding capacity" (BC) of A-P had to be precisely adjusted at different stages of gestation, to control Pu with "razor's-edge" precision. The present study is an attempt to achieve this precision.

Material and methods

All techniques used in this study have been described in detail in an earlier report.[5]

1. Preparation of A-P. Briefly stating, A-P was raised in rabbits by treatment with progesterone 11-α-hemisuccinate, coupled to bovine serum albumin. Antisera from rabbits showing high specificity for P and a "binding capacity" (BC) of at least 3 μg of P per milliliter were selected and pooled. The pooled antisera were partially purified and concentrated by precipitation with ammonium sulfate at 40 per cent saturation. The stock solution contained 70 mg. of protein per milliliter and its BC was 15 μg of P per milliliter. Given in a single dose of 2 ml, this concentrated A-P solution was expected to reduce Pu effectively at day 6 of gestation.

2. Measurements of A-P, Pt, and Pu. A-P was assayed by measuring the binding of P to A-P with the dextran-coated charcoal method, incubating 1,000 to 10,000× diluted plasma samples with 5×10^{-8}M tritiated P (84 Ci/mM, Amersham). The concentration of A-P was expressed as micrograms of P per milliliter of BC (Fig. 1).

Pt was measured by RIA; Pu was calculated, knowing the concentrations of A-P, Pt, and the value of Kop (Kop = $10^8 M^{-1}$), a constant which characterizes the binding of P to A-P in plasma.[5]

3. Animals, A-P treatment, and blood collection. Since each gestating rat was to receive 2 ml. of A-P (30 μg of P, BC) and since this concentrated A-P was available only in the limited quantity of 150 μg of P, BC (commercial price $6,000), the experiments had to be restricted to five experimental and six control rats. At

day 6 of gestation the animals weighed 246 ± 5 grams and had an average litter of 11 ± 1. Before A-P treatment at 9 A.M., 1 ml. of blood was collected from the tail veins of each animal and centrifuged at 0° C. and the plasmas were stored at −20° C. After the collection of the first plasma sample, each rat received 2 ml. of A-P intraperitoneally and yielded 1 ml. of blood sequentially at 3, 6, 24, 48, and 96 hours after A-P treatment. Of these five animals, three were bleeding 24 hours after A-P treatment and stopped gaining weight; the remaining two did not bleed and continued to gain weight. Since these symptoms indicated that the former rats will abort and the latter two will not, two groups of animals were formed.

The six control animals were exposed to the same treatment as the experimental rats except that, instead of A-P, they received 2 ml. of rabbit serum. At day 10 of pregnancy, the six control and five experimental rats were anesthetized and the conceptus sacs (when present) were removed and weighed. The results were tabulated and analyzed for statistically significant differences.

Results

As illustrated by Fig. 1, *A*, between days 6 and 10 of gestation, the six control rats had a slight but significant decrease in circulating plasma P from 74 ± 3 to 47 ± 2 ng. per milliliter ($P > 0.001$). Of course, this physiologic Pw had no effect on normal pregnancy maintenance. In contrast, as the plasma levels of A-P in the experimental rats increased to a peak value of 1,209 ± 32 ng. per milliliter (BC), 839 ± 68 ng. per milliliter of Pt were bound by A-P (3 to 6 hours after treatment) and thus Pu decreased to 8 ± 1 ng. per milliliter ($P > 0.001$). Subsequently Pu remained below 10 ng. per milliliter throughout the entire observation period, despite the steady decrease in both A-P and Pt, indicating that drastic and lasting Pw (below 86 per cent) irreversibly damaged P genesis. At 24 hours after A-P treatment bleeding signaled inevitable abortion, confirmed at day 10.

The remaining two rats (Fig. 1, *B*), in which the initial A-P concentrations were lower than in the Fig. 1, *A* animals and in which Pt withdrawal lagged behind A-P withdrawal, had only a transient but significant decrease in Pu to 35 ± 9 ng. per milliliter ($P > 0.001$) and sustained pregnancy. However, when examined at day 10, the weight of their conceptuses was only 50 ± 2 mg., whereas that of the six controls was 67 ± 1 mg. ($P > 0.001$). Of course, the uteri of those rats which aborted were empty, or contained only a small pulpy mass. A possible explanation for these differences between Figs. 1, *A* and *B*, rats (treated with the same A-P dose) might have been slower intraperitoneal absorption of A-P in the Fig. 1, *B* animals. This could account for the consequent escape of Pu from excessive binding. However, it is fortunate that these differences were encountered, since they exposed the *strictly quantitative* nature of the relationship between A-P and Pu on the one hand and between Pu and pregnancy maintenance on the other.

Together the results demonstrated that pregnant rats with normal P levels have normal conceptuses, those with partly and transiently reduced Pu levels have retarded conceptuses, and animals with drastically and permanently reduced Pu levels abort. Thus, while between days 6 and 10 of gestation, Pw did occur in *all* (control as well as experimental) animals, pregnancy was intact if Pw reached only 47 ± 2 ng. per milliliter, the conceptuses had retarded growth if the nadir was only 35 ± 9 ng. per milliliter, and the mothers aborted if Pw reached 8 ± 1 ng. per milliliter.

Comment

At day 10 of gestation, normal pregnancy has been invariably terminated in the rat "model"[5] by reducing Pu from 55 ± 2 to 16 ± 3 ng. per milliliter, with an A-P dose which bound only 6 μg of P. In contrast, the same dose of A-P at day 6 of gestation reduced Pu only from 67 ± 4 to 41 ± 1 ng. per milliliter, a moderate change which did not affect normal pregnancy. However, this same treatment did provoke abortion if, prior to A-P treatment, plasma P had been lowered to "half mast" by unilateral ovariectomy, which by itself does not terminate pregnancy.[5]

In the present study a five times higher A-P dose has been administered at day 6 of gestation. When this massive A-P dose, capable of binding 30 μg of P, reduced Pu from 74 ± 3 to 8 ± 1 ng. per milliliter pregnancy terminated. However, when (due to slow absorption) this same dose of A-P only transiently reduced Pu to 35 ± 9 ng. per milliliter, pregnancy continued and only retarded conceptus growth reflected that Pw had an effect. Apparently, at different stages of gestation, the mechanisms of the A-P and Pw actions are the same, but the *critical* values to which Pu has to be reduced (to terminate pregnancy) are different and so are the *doses of A-P* which predictably achieve effective Pw.

It is of considerable interest that five times more A-P is needed to provoke an only moderately greater Pw at day 6 than at day 10 and that even this massive A-P dose fails occasionally to induce effective Pw and abortion. These findings expose the *strictly quantitative* nature of the relationship between P levels and pregnancy maintenance on the one hand and the razor's-

edge precision which has to be achieved in altering P levels for the predictable control of pregnancy on the other. The reason behind the different efficacy of A-P at day 6 and 10 of pregnancy is not established definitively. However, it is likely that the corpora lutea respond to the reduction of Pu with increased P secretion and that at day 6 this "compensatory" potential is greater than at day 10. In any case, plasma levels alone do not define the effective A-P dose quantitatively. Thus, P-secretion rates and other factors (binding at target sites, local effect, metabolism, etc.) have to be considered in calculating that A-P dose, which predictably reduces Pu to the *critical* abortion value. It is of further interest that partial and transient Pw retards conceptus growth, a finding which has to be further investigated to be confirmed.

The strictly quantitative relationship between P and pregnancy maintenance is well established in human patients (for references see Csapo[3]). Studies during early pregnancy in over 50 luteectomized women revealed that, if during 3 days after luteectomy continued Pw reaches 3.1 ± 0.5 ng. per milliliter, the patients abort (without therapeutic stimulation) when P decreases below 3 ng. per milliliter at 3.8 ± 0.2 days after surgery. If Pw reaches only 4.3 ± 0.8 ng. per milliliter the patients develop the symptoms of imminent abortion at day 6.4 ± 0.3, whereas if Pw fails to continue below 9.7 ± 1.4 ng. per milliliter at day 4 after luteectomy then pregnancy is maintained. However, while in 6 weeks pregnant women (Nagele) the abortion value is below 3 ng. per milliliter if pregnancy is terminated by luteectomy, it is 10.7 ± 0.7 in 9.4 ± 0.2 weeks pregnant and 20.3 ± 1.5 ng. per milliliter in 16.3 ± 0.4 weeks pregnant patients if abortion is provoked by the "double prostaglandin impact." Premature delivery during the 35 ± 1 weeks of pregnancy has been observed at 71 ± 6 ng. per milliliter and normal spontaneous labor during the 39.3 ± 0.4 weeks of gestation at 141 ± 6 ng. per milliliter P levels.

Of course, as described in the see-saw theory,[3] these critical values of P, at which pregnant women abort at different stages of gestation and deliver prematurely or normally, are strongly affected by therapeutic stimulants which amplify the action of the intrinsic stimulants. Effective therapeutic stimulation permits pregnant patients to abort or deliver at moderately higher P values than those gravidas who are entirely dependent on intrinsic myometrial stimulation. Nevertheless, at all stages of gestation a *critical* degree of Pw is demanded for pregnancy termination, to reduce *threshold* and thus convert the uterus from a *refractory* to a *reactive* organ.[6] Only the converted uterus can respond to endogenous or exogenous stimuli with high-level cyclic intrauterine pressure. The experiments described in this report, when continued and extended, may further clarify and quantitatively define both the regulatory "balance" and "imbalance" of the pregnant uterus and in so doing promote conceptual advances in reproductive medicine.

The authors are grateful to Elise F. Csapo and Gabriele Salau for their dedicated assistance and to Wynne Stifel for her help in the manuscript.

REFERENCES

1. Corner, G. W., and Allen, W. M.: Physiology of the corpus luteum. VII. Maintenance of pregnancy in rabbit after very early castration, by corpus luteum extracts, Proc. Soc. Exp. Biol. Med. **27:** 403, 1930.
2. Csapo, A. I.: *In* Laki, editor: Contractile Proteins and Muscle, New York, 1961, Marcel Dekker, Inc., Chap. 14, p. 413.
3. Csapo, A. I.: The "see-saw" theory of the regulatory mechanism of pregnancy, Am. J. Obstet. Gynecol. **121:** 578, 1975.
4. Raziano, J., Ferin, M., and Vande Wiele, R. L.: Effect of antibodies to estradiol-17β and to progesterone on nidation and pregnancy in rats, Encocrinology **90:** 1133, 1972.
5. Csapo, A. I., Dray, F., and Erdos, T.: The biological effects of injected antibodies to estradiol-17β and to progesterone in pregnant rats, Endocrinology **97:** 603, 1975.
6. Csapo, A. I., Herczeg, J., Pulkkinen, M., Kaihola, H. L., Zoltan, I., Csillag, M., and Mocsary, P.: Termination of pregnancy with double prostaglandin impact, Am. J. Obstet. Gynecol. **124:** 1, 1976.

Hepatitis B antigen: A review of its importance in the practice of obstetrics and gynecology

RICHARD R. BABB, M.D.

Palo Alto, California

Surgeons engaged in the practice of obstetrics and gynecology should have a clear understanding of the hepatitis B antigen (Australia antigen) serologic test. When positive, it serves as a marker either for the carrier state or for subclinical to overt hepatitis B (serum hepatitis). Patients or health personnel with a positive test are potentially infectious and appropriate precautions should be taken. Surgeons are at increased risk for hepatitis B and, when acutely exposed, should receive standard serum globulin, or perhaps high-titer hepatitis B immune globulin in the future. Infants born to mothers with a positive test may become hepatitis B antigen positive and develop chronic hepatitis. (AM. J. OBSTET. GYNECOL. 126: 602, 1976.)

AN INCREASINGLY common serologic test in clinical medicine is for the so-called Australia antigen or hepatitis B antigen (HB Ag). The implications of a positive result in management of patients can be confusing. Thus, this article has been written with two purposes in mind; (1) to briefly review the concept of the hepatitis B antigen and its relation to viral hepatitis and (2) to stress its unique clinical importance to surgeons practicing obstetrics and gynecology.

Based on epidemiologic, clinical, and laboratory data over the past 30 years, it has become clear that there are two types of viral hepatitis, e.g., infectious hepatitis or hepatitis A and serum hepatitis or hepatitis B.[1-5] The latter was initially felt to be transmitted parenterally, by either injection or blood transfusion. Case reports began to suggest, however, that hepatitis B could also be transmitted via nonparenteral routes.[3] Krugman, Giles and Hammond,[2] in a series of clinical experiments at Willowbrook State School in New York, showed that their MS-2 strain of virus which caused hepatitis B was infective by mouth.[4]

In 1964 and 1965 Blumberg, Alter, and Visnich[6] reported finding an isoprecipitin or antibody in the serum of a patient with hemophilia who had received multiple blood transfusions. This antibody was noted to react with one of the panel sera from an Australian aborigine, which was labeled the Australia antigen. Numerous studies have since shown the Australia antigen to be closely associated with, or the virus of, hepatitis B.[4, 7, 8]

The Australia antigen can be found in patients' blood with various serologic techniques such as complement fixation, immunoelectrophresis, and radioimmunoassay. It also can be demonstrated by immune electron microscopy, which has shown three types of particles representing the Australia antigen.[8, 9] The larger particles, or so-called Dane particles can be separated into two components—an outer coat with Australia antigen activity (surface antigen) and an inner core (core antigen). Antibodies have been found in the sera of patients with hepatitis B which react with each component.[10]

At this point, nomenclature should be clarified. Over the past decade various names have been substituted for Australia antigen including SH antigen, hepatitis-associated-antigen, Au (1), and HB Ag.[7] Currently, the following abbreviations are often used[10]: HB_s Ag: hepatitis B surface antigen; HB_c Ag: hepatitis B core antigen; anti-HB_s: antibody to HB_s antigen; and anti-HB_c: antibody to HB_c antigen.

Hepatitis B antigen

The carrier state. HB Ag has been demonstrated not only in patients with acute and chronic hepatitis but also in presumably healthy people.[7, 11, 12] The incidence of HB Ag carriers in blood donor volunteers ranges from 0.1 to 0.5 per cent.[13, 14] Since HB Ag has been demonstrated in blood, saliva, feces, urine, bile,

From the Section of Gastroenterology, Palo Alto Medical Clinic and the Stanford University School of Medicine.

Reprint requests: Richard R. Babb, M.D., Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto, California 94301.

and semen,[15] management of the asymptomatic, but nonetheless potentially infectious, carrier has assumed considerable importance. Mosley calls these carriers a potential "new kind of leper."[16] Cases of hepatitis B have been transmitted to patients by doctors, nurses, dentists, and other health personnel.[16–21] Outbreaks have been related to sexual contact,[22–24] and there appears to be a higher incidence of HB antigen and antibody in families of carriers as compared to control households.[25] However, communicability is not as great as once feared.[20] In a recent report, Alter and associates[26] followed 228 patients for 6 to 9 months who had been in contact with medical personnel positive for HB_s Ag. The incidence of subsequent hepatitis B was the same in the exposed group as in the controls.

After thorough evaluation, most carriers of HB Ag show no signs of serious liver disease. In a review of 82 healthy carriers subjected to liver biopsy, Griffin[11] noted the importance of liver function tests. Almost half of those with normal tests had normal biopsies, and none showed evidence of serious hepatitis. All of those with abnormal liver function had abnormal biopsies, and two showed signs of serious, or so-called chronic aggressive, hepatitis. Feinman and associates[27] followed 115 asymptomatic carriers (volunteer blood donors) over a mean time of 18 months. Approximately one half had normal liver function tests, and none of these showed serious hepatitis on biopsy. Biopsies done on 11 carriers with abnormal liver function tests were all abnormal, although only one showed aggressive hepatitis. During the period of observation, these patients showed no evidence of clinical or histologic deterioration.

My practice is to inform the healthy carrier that he or she is potentially infectious and should observe appropriate precautions relative to the use of toilet articles and personal hygiene. A carrier cannot donate blood. If liver function tests are normal, I do not think liver biopsy is required; if tests are abnormal over a 3 to 6 month follow-up period, then a biopsy should be done to rule out serious underlying liver disease. Health personnel, including doctors, should be treated in similar fashion and not excluded from patient care.[28] Future surveillance of such carriers and their contacts is mandatory.

Risk to the surgeon. Viral hepatitis is an occupational hazard for medical personnel.[28–32] Surgeons, laboratory technicians, and especially those assigned to dialysis and oncology units are at risk. Three of 16 cases in hospital personnel reported from Memphis over a 3 year period were in surgeons.[29] Four surgeons, after operating on a HB Ag–positive patient, later developed clinical or laboratory evidence of hepatitis B.[30] Jordan[31] has labeled hepatitis "the surgeon's disease," and notes that 5 per cent of the Baylor University surgical house staff suffer with it yearly.

As noted above, HB Ag has been found in most body fluids. Villarejos and associates[33] identified HB Ag in the saliva of 76 per cent of patients with acute hepatitis B and in 86 per cent of carriers—leading them to write "saliva is probably the main vehicle of infection in nonparenterally acquired Type B hepatitis." Less than 0.0001 c.c. of infected blood can produce hepatitis,[31] and it has been estimated that a majority of surgeons have holes in their gloves after operations.[30] All of this points out the unique hazards for surgeons of contacting hepatitis B.

In order to lower this risk I recommend the following:

1. Patients with a history of "liver disease," hepatitis, blood transfusions, drug abuse, or intimate exposure to others with hepatitis should be screened for HB Ag. If positive, they should be advised as noted above.

2. Hospitalized HB Ag-positive patients should be isolated, and their body fluids and blood clearly labeled and handled with great caution. Protective clothing should be worn by all medical personnel. Contaminated equipment can be autoclaved or sterilized by boiling, and surfaces can be cleaned with soap and water to be followed by the use of germicidal solutions such as hypochlorite[35, 36] or glutaraldehyde. An excellent review of general measures that should be practiced in the hospital to prevent hepatitis B has recently been published.[28]

3. The use of standard serum globulin or hepatitis B immune globulin should be considered. Although standard gamma-globulin preparations tend to have low hepatitis B antibody titers, products manufactured since 1972 have higher titers and have been effective in preventing hepatitis B after "low-level exposure."[37, 38] Recent studies have shown high titer hepatitis B antibody gamma globulin to also be effective in preventing or at least modifying hepatitis B.[38–43] Soldiers receiving 5 or 10 c.c. of this special gamma globulin prophylactically showed protection against the later development of icteric hepatitis.[42] Prince and associates[39] administered serum hepatitis immune globulin to retarded children at a dose level of 0.01 c.c. per 0.5 kilogram of body weight before exposure to hepatitis B in an endemic setting.[43] They found a decreased incidence of both hepatitis and the carrier state. In addition to the above, Krugman, Giles, and Hammond[40] and Krugman and Giles[41] found the specially prepared gamma globulin to be effective when given 4 hours

after exposure to hepatitis B virus in mentally retarded children at the Willowbrook State School in New York. After receiving a dose of 0.02 c.c. per pound of body weight, their patients showed a decreased rate of clinical hepatitis and HB Ag carrier state as compared to controls. They stated the dose of virus administered was similar to that from a contaminated needle. It should be noted that the titer of hepatitis B antibody (anti-HB_s) in these special gamma globulin preparations is 50,000 to 200,000 times that of those commercially available.

In an editorial,[37] experts from the National Institutes of Health have recommended that persons contaminated by blood or secretions which are HB_s Ag positive receive standard serum globulin until the high-titer hepatitis B globulin becomes more available.

Several authorities have expressed reservations about the use of these high-titer products, pointing out that the attenuation of the immune response may lead to a more prolonged carrier state and chronic hepatitis.[43, 44] Krugman and Giles[41] have thus far not found this to be the case.

Blood transfusion. It has been estimated that the incidence of transfusion hepatitis can be decreased by at least 25 per cent if blood donors are routinely screened for HB Ag.[13, 14] As might be expected, patients with pre-existing hepatitis B antibody (anti-HB_s) have a lower incidence of transfusion hepatitis than those who are negative.[14]

Some patients, however, become ill with hepatitis B after transfusions despite receiving HB Ag-negative blood.[14] This may be due to screening methods which do not pick up minute quantities of the hepatitis B virus. Remembering the discussion above about the surface and core hepatitis B antigens and antibody, it should be noted that currently most laboratories screen only for the surface antigen (HB_s Ag) and corresponding antibody (anti-HB_s). Hoofnagle and associates[10] described one instance where blood positive for antibody to the hepatitis B core antigen (anti-HB_c) and negative for surface antigen and antibody (HB_s Ag and anti-HB_s) probably led to hepatitis B in the recipient.

Using the latest screening techniques, two groups have recently shown that some cases of posttransfusion hepatitis are presumably not due to either hepatitis A or B.[45, 46] Other infectious agents (? hepatitis C virus) may be candidates.

HB Ag and its relationship to the neonate and infant. I have already discussed the fact that HB Ag is a marker for hepatitis B infection, and thus carriers are potentially infectious and should be treated as such. When the carrier is a mother, hospitalized for delivery, precautions noted above should be followed.

Infants born to mothers who are either HB Ag carriers or ill with hepatitis B may become HB Ag positive and develop chronic hepatitis. Schweitzer and associates,[47, 48] reporting on their large experience at Los Angeles County Hospital, found that the risk of a neonate becoming HB Ag positive depended on the stage of intrauterine development when exposure to the virus occurred. Twenty-one mothers were asymptomatic carriers, and only one baby was HB Ag positive. Of six mothers with acute hepatitis B during the first trimester, none of the neonates was positive. Eleven mothers became ill during the last trimester, and seven of these babies were HB Ag positive. Thus, acute hepatitis B near term was associated with the highest risk.

Stevens and associates[49] studied the transmission of HB_s Ag from mothers, who were carriers but otherwise healthy, to their offspring. Of 158 babies, 63 (40 per cent) became antigen positive within a few months of birth, a much higher result than that noted in Los Angeles. The reason for this is not clear. Three factors appeared to increase the chance of developing antigenemia in these babies, e.g., the HB_s Ag titer in the mother's blood, the presence of HB_s Ag in cord blood, and a positive HB_s Ag test in siblings' blood.

The route of infection is related to both transplacental transmission of the virus and ingestion of contaminated material at the time of delivery. The antigen has also been found in breast milk, although this is probably not a means of transmission.[50]

Once HB Ag positive, the infants generally remain so. In the Taiwan study,[49] 35 of 38 babies (92 per cent) remained positive over a follow-up period averaging 7.5 months. Schweitzer and associates[47] followed the course of 15 HB Ag–positive infants. Two developed acute hepatitis B at ages 8 and 12 weeks with subsequent complete recovery and conversion of the HB Ag test to negative. The others have shown a persistent HB Ag–positive state and elevated liver enzymes over a 4 to 30 month observation period. Liver biopsies were done on ten. All revealed evidence of unresolved hepatitis, and one had associated portal fibrosis (age 16 months).

Merrill, Dubois, and Kohler[51] have described four HB Ag–positive infants born to mothers with acute hepatitis B near the time of delivery or soon thereafter. All have stayed positive, with elevated serum transaminase levels over an 8 to 22 month period.

At present the long-term prognosis in these infants is not known; nonetheless, a persistent carrier state and chronic liver disease extending into adulthood is a distinct possibility. Just as the specific high titer HB antibody (anti-HB_s) globulin has been administered to

prevent or modify hepatitis B in adults, it has also been used in neonates. Kohler and associates[52] gave such a preparation to four infants born to HB Ag–positive mothers within 2 to 6 days of birth. All four remained HB Ag negative at 5 to 16 months. Six of seven similar babies, not treated, became HB Ag positive at 5 to 12 weeks post partum. One baby given standard gamma globulin likewise became HB Ag positive. If the above results are substantiated in future studies, and if the specific high-titer globulin becomes more available, it may become standard practice to administer high-titer HB antibody globulin to babies of HB Ag-positive mothers.

REFERENCES

1. Iber, F., and Mendeloff, A. I.: Prevention and treatment of viral hepatitis, Arch. Intern. Med. **109:** 310, 1962.
2. Krugman, S., Giles, J. P., and Hammond, J.: Infectious hepatitis, J. A. M. A. **200:** 365, 1967.
3. Koff, R. S., and Isselbacher, K. J.: Changing concepts in the epidemiology of viral hepatitis, N. Engl. J. Med. **278:** 1371, 1968.
4. Giles, J. P., McCollum, R. W., Berndtson, L. W., and Krugman, S.: Viral hepatitis: Relation of Australia/SH antigen to the Willowbrook MS-2 strain, N. Engl. J. Med. **281:** 119, 1969.
5. Editorial: More about Australia antigen and hepatitis, Lancet **1:** 347, 1970.
6. Blumberg, B., Alter, H. J., and Visnich, S.: A "new" antigen in leukemia sera, J. A. M. A. **191:** 541, 1965.
7. Blumberg, B. S., Sutnick, A., London, W. T., and Millman, I.: Australia antigen and hepatitis, N. Engl. J. Med. **283:** 349, 1970.
8. Dane, D. S., Cameron, C. H., and Briggs, M.: Virus-like particles in serum of patients with Australia-antigen-associated hepatitis, Lancet **1:** 695, 1970.
9. Almeida, J. D., Rubenstein, D., and Stott, E. J.: New antigen-antibody system in Australia-antigen-positive hepatitis, Lancet **2:** 1225, 1971.
10. Hoofnagle, J. H., Gerety, R. J., Ni, L. Y., and Barker, L. F.: Antibody to hepatitis B core antigen, N. Engl. J. Med. **290:** 1336, 1974.
11. Griffin, F. M.: Hepatitis B antigenemia in apparently healthy blood donors, J. A. M. A. **226:** 753, 1973.
12. Chalmers, T. C., and Alter, H. J.: Management of the asymptomatic carrier of the hepatitis-associated (Australia) antigen, N. Engl. J. Med. **285:** 613, 1971.
13. Goche, D. J.: A prospective study of post-transfusion hepatitis, J. A. M. A. **219:** 1165, 1972.
14. Alter, H. J., Holland, P. V., Purcell, R. M., Lander, J. J., Feinstone, S. M., Morrow, A. G., and Schmidt, P. J.: Post-transfusion hepatitis after exclusion of commercial and hepatitis-B antigen-positive donors, Ann. Intern. Med. **77:** 691, 1972.
15. Heathcote, J., Cameron, C. H., and Dane, D. S.: Hepatitis-B antigen in saliva and semen, Lancet **1:** 71, 1974.
16. Mosley, J. W.: The HBV carrier—A new kind of leper? N. Engl. J. Med. **292:** 477, 1975.
17. Williams, S. V., Huff, J. C., Feingloss, E. J., Gregg, M. B., Hatch, M. H., and Matsen, J. M.: Epidemic viral hepatitis, type B, in hospital personnel, Am. J. Med. **57:** 904, 1974.
18. Feldman, R. E., and Schiff, E. R.: Hepatitis in dental professionals, J. A. M. A. **232:** 1228, 1975.
19. Vaisrub, S.: Hepatitis B—Traffic in the dentist's office, J. A. M. A. **232:** 1270, 1975.
20. Redeker, A. G.: Hepatitis B. Risk of infection from antigen-positive medical personnel and patients, J. A. M. A. **233:** 1061, 1975.
21. Grob, P. J., and Moeschlin, P.: Risk to contacts of a medical practitioner carrying Hbs Ag, N. Engl. J. Med. **293:** 197, 1975.
22. Fass, R. J.: Sexual transmission of viral hepatitis? J. A. M. A. **230:** 861, 1974.
23. Wright, R. A.: Hepatitis B and HB_sAg carrier, J. A. M. A. **232:** 717, 1975.
24. Szmuness, W., Much, M. I., Prince, A. M., Hoffnagle, J. H., Cherubin, C. E., Harley, E. J., and Block, G. H.: On the role of sexual behavior in the spread of hepatitis B infection, Ann. Intern. Med. **83:** 489, 1975.
25. Szmuness, W., Prince, A. M., Kirsch, R. L., and Brotman, B.: Familial clustering of hepatitis B infection, N. Engl. J. Med. **289:** 1162, 1973.
26. Alter, H. J., Chalmers, T. C., Freeman, B. M., Lunceford, J. L., Lewis, T. L., Holland, P. V., Pizzo, P. A., Plotz, P. H., and Meyer, W. J.: Health-care workers positive for hepatitis B surface antigen, N. Engl. J. Med. **292:** 454, 1975.
27. Feinman, S. V., Cooter, N., Sinclair, J. C., Wrobel, D. M., and Berris, B.: Clinical and epidemiological significance of the HB_sAg (Australia antigen): Carrier state, Gastroenterology **68:** 113, 1975.
28. Snydman, D. R., Bryan, J. A., and Dixon, R. E.: Prevention of nosocomial viral hepatitis, Type B (hepatitis B), Ann. Intern. Med. **83:** 838, 1975.
29. Trumbull, M. L., and Greiner, D. J.: Homologous serum jaundice: An occupational hazard to medical personnel, J. A. M. A. **145:** 965, 1951.
30. Rosenberg, J. L., Jones, D. P., Lipitz, L. R., and Kirsher, J. B.: Viral hepatitis: An occupational hazard to surgeons, J. A. M. A. **223:** 395, 1973.
31. Jordan, G. L.: Hepatitis—The surgeon's disease, Am. J. Surg. **127:** 629, 1974.
32. Wands, J. R., Chura, C. M., Roll, F. J., and Maddrey, W. C.: Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders, Gastroenterology **68:** 105, 1975.
33. Villarejos, V. M., Visona, K. A., Gutierrez, A., and Rodriguez, A.: Role of saliva, urine and feces in the transmission of type B hepatitis, N. Engl. J. Med. **291:** 1375, 1974.
34. Barker, L. F., Shulman, R., Murray, R., Hirschman, R. J., Ratner, F., Diefenbach, W. C. L., and Geller, H. M.: Transmission of serum hepatitis, J. A. M. A. **211:** 1509, 1970.
35. Bryan, J. A.: Hypochlorite solutions and viral hepatitis, J. A. M. A. **230:** 961, 1974.
36. Bond, W. W., and Pattison, C. P.: Control of hepatitis B virus in environmental contamination, J. A. M. A. **231:** 700, 1975.
37. Alter, H. J., Barker, L. F., and Holland, P. V.: Hepatitis B immune globulin: Evaluation of clinical trials and rationale for usage, N. Engl. J. Med. **293:** 1093, 1975.
38. Iwarson, S., Ahlmen, J., Eriksson, E., Hermodsson, S., Kjillman, H., Ljunggren, C., and Selander, D.: Hepatitis B immune serum globulin and standard gamma globulin in prevention of hepatitis B infection among hospital staff: A preliminary report, Am. J. Med. Sci. **270:** 385, 1975.

39. Prince, A. M., Szmuness, W., Woods, K. R., and Grady, G. F.: Antibody against serum-hepatitis antigen, N. Engl. J. Med. **285:** 933, 1971.
40. Krugman, S., Giles, J. P., and Hammond, J.: Viral hepatitis, type B (MS-2 strain): Prevention with specific hepatitis B immune serum globulin, J. A. M. A. **218:** 1665, 1971.
41. Krugman, S., and Giles, J. P.: Viral hepatitis, type B (MS-2 strain): Further observations on natural history and prevention, N. Engl. J. Med. **288:** 755, 1973.
42. Ginsberg, A. L., Conrad, M. E., and Bancroft, W. M.: Prevention of endemic HAA-positive hepatitis with gamma globulin: Use of a simple radioimmune assay to detect HAA, N. Engl. J. Med. **286:** 562, 1972.
43. Szmuness, W., Prince, A. M., Goodman, M., Ehrich, C., Pick, R., and Ansari, M.: Hepatitis B immune serum globulin in prevention of nonparenterally transmitted hepatitis B, N. Engl. J. Med. **290:** 701, 1974.
44. Alter, H. J., Holland, P. V., Schmidt, P. J., and Plotz, P. H.: Gamma-globulin for hepatitis-virus B. Prevention or extension? Lancet **1:** 1110, 1972.
45. Prince, A. M., Grady, G. F., Hazzi, C., Broman, B., Kuhns, W. J., Levine, R. W., and Millian, S. J.: Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis-B virus, Lancet **2:** 241, 1974.
46. Feinstone, S. M., Kapikian, A. Z., Purcell, R. H., Alter, H. J., and Holland, P. V.: Transfusion-associated hepatitis not due to viral hepatitis Type A or B, N. Engl. J. Med. **282:** 767, 1975.
47. Schweitzer, I. L., Dunn, A. E. G., Peters, R. L., and Spears, R. L.: Viral hepatitis B in neonates and infants, Am. J. Med. **55:** 762, 1973.
48. Schweitzer, I. L., Mosley, J. M., Achcavai, M., Edwards, V. M., and Overby, L. B.: Factors influencing neonatal infection by hepatitis B virus, Gastroenterology **65:** 277, 1973.
49. Stevens, C. E., Beasley, R. P., Tsui, J., and Lee, W.: Vertical transmission of hepatitis B antigen in Taiwan, N. Engl. J. Med. **292:** 771, 1975.
50. Linnemann, C. C., and Goldberg, S.: HB Ag in breast milk, Lancet **2:** 155, 1974.
51. Merrill, D. A., Dubois, R. S., and Kohler, P. F.: Neonatal onset of the hepatitis-associated-antigen carrier state, N. Engl. J. Med. **287:** 1280, 1972.
52. Kohler, P. F., Dubois, R. S., Merrill, D. A., and Bowes, W. A.: Prevention of chronic neonatal hepatitis B virus infection with antibody to the hepatitis B surface antigen, N. Engl. J. Med. **291:** 1378, 1974.

Inaugural meeting—National Perinatal Association

The inaugural meeting of the National Perinatal Association will be held December 1-4, 1976, at Stouffer's Riverfront Towers, 200 S. Fourth St., St. Louis, Missouri 63102. The theme will be "Perinatal Priorities." This meeting is for physicians, nurses, social workers, nutritionists, and others involved in perinatal care. It will include presentations and small groups working on problems in perinatal care and the development of priorities. For further information, contact: Stanley N. Graven, M.D. (605-336-3440), National Perinatal Association, 1100 S. Euclid Ave., Sioux Falls, South Dakota 57105.

CORRESPONDENCE

Oral contraceptives and thromboembolism

To the Editors:

Goldzieher and Dozier's assertion (AM. J. OBSTET. GYNECOL. 123: 878, 1975) that our calculations[1] of the relative risk of venous thrombosis "must be incorrect" is as outrageous as it is inaccurate. Since they attempt to estimate our denominator by dividing *observed* numbers by *standardized* rates, it is hardly surprising that they cannot reconcile their figures with ours.

I must state categorically that there is no arithmetical error in any of our tabulations. Goldzieher and Dozier have used my letter of November, 1974[2] to cast doubt on all our results. I indicated then that the way in which allowances are made in the calculations for patients with conditions predisposing to venous thrombosis is necessarily arbitrary. In our report data we took account of what we believed were the important predisposing causes in respect of which there were differences between Takers and Controls. The number of these (after the exclusion of pregnancy) was quite small, so that their exclusion had a negligible effect on the respective denominators. The point of my letter was to indicate that we were about to recalculate our data with a much more rigorous set of assumptions about predisposing causes and, indeed, to exclude from the Taker, Ex-Taker, and Control groups every condition that could even remotely have bearing on the development of venous thrombosis. The fact that these new calculations, which I[3] briefly reported last year, left the relative risks almost unchanged merely indicates that we have previously already made allowance for the conditions that mattered.

I sympathize with Goldzieher and Dozier's predicament in that our new calculations were published after they had completed their draft. Nevertheless, they were able to refer to them in a footnote, and, since the results have (or should have) such an important influence on their entire paper, it is disappointing that the authors could not have changed their text or at least their summary to indicate that the doubts which they had raised about our previous results had now been resolved.

Clifford R. Kay, M.D., Ph.D., F.R.C.G.P.
Recorder, Oral Contraception Study
8 Barlow Moor Road
Manchester M20 OTR, England

REFERENCES

1. Royal College of General Practitioners: Oral Contraceptives and Health, London, 1974, Pitman Medical.
2. Kay, C. R.: Oral contraceptives and health: Thromboembolic disease, Lancet **2:** 1138, 1974.
3. Kay, C. R.: Oral contraceptives and venous thrombosis, Lancet **1:** 1381, 1975.

To the Editors:

I was interested to read in the JOURNAL, the "Current Developments" article, "Oral contraceptives and thromboembolism: A reassessment," by Joseph W. Goldzieher, M.D., and Tazewell S. Dozier. The long, detailed and technical review by a respected clinical and laboratory investigator would infer a rather accurate and definitive current assessment of this important subject. However, the article is unbalanced in its presentation with forceful and frequently unjustified attacks on retrospective controlled studies in contrast to a benign, if not complimentary, review of noncontrolled "Phase III" trials and a rather small-scale prospective study conducted in Pureto Rico. I would like to mention below only some of the faults found with this article. A few examples of technical errors are cited, and the authors' rather selected, if not biased, interpretation of biological and methodologic considerations is rebutted.

Regarding errors, at the bottom of page 894, the authors cite a threefold *decrease* in the use of oral contraceptives in a second sample of controls included in the 1969 Vessey and Doll (Reference 74, Goldzieher and Dozier) study as compared to an earlier sample, but on the next page the reverse is specified.

On page 896, an argument is developed which is irrelevant. The authors calculate confidence limits around the proportion of oral contraceptive users in a control group included in The Johns Hopkins Cooperating Hospitals study (Reference 60, Goldzier and Dozier), in which Dr. Sartwell was Director and I was Co-Director. More specifically, the per cent of oral contraceptive users among the control group was 14.8 with 95 per cent confidence limits of 8.2 to 25.6 per cent (or 0.082 to 0.256). The latter confidence limits were then compared to a hypothetical incidence of idiopathic thromboembolic disease in the general population of 0.05 cases per *thousand* women per year, which is based on assumptions that cannot be made from our study as explained in a separate letter by Dr. Sartwell. The lower confidence limit of control oral contraceptive usage (0.082) was stated to be "still significantly higher" than the hypothetical population *incidence* of 0.05 (which is not a per cent but an annual rate per thousand women). This statement says that an assumed rate of idiopathic thromboembolism, and

even total thromboembolism, is less than the *prevalence* of oral contraceptive usage in a control group; such comparison is meaningless. Is it possible that the authors intended to imply freedom from thromboembolism risk during oral contraceptive usage by claiming that a higher proportion of control subjects used oral contraceptives than experienced thromboembolism? The relative infrequency of thromboembolism in the general population is accepted and bears no relationship to the specific risks among oral contraceptive users and nonusers. The latter example is one of many unjustified arguments raised in this article.

The authors imply that risks of rare, serious thromboembolic events occurring in otherwise healthy women using oral contraceptives, e.g., idiopathic cerebrovascular syndromes, myocardial infarction, and pulmonary embolism, could be determined in populations of as few as several thousand women using and not using the oral contraceptives (with the assumption of a relative risk of five). First of all, the annual incidence of these serious, rare events is not one or two per thousand, as it may be for all forms of primary and secondary thromboembolism, but rather tenfold to a hundredfold less frequent. Thus, the population size required for a prospective study would need to be multiplied by a factor of at least tenfold. Such size requirements are far greater than those of any of the prospective studies which the authors claim to be adequate. Furthermore, the estimations of required numbers of subjects needed to detect a certain risk assume that the outcome is completely and specifically detectable. More simply stated, for example, ten occurrences in a user group of 1,000 versus none in a control group of 1,000 would be highly significant (chi square = 10.05; $P < 0.005$). However, an *excess* of ten cases associated with the same exposure would not be statistically significant if four times as many cases (or 40) of nonattributable "secondary" disease occurred in *each* population, i.e., 50 versus 40 (chi square = 1.16; $P > 0.20$). Thus, the majority of cases of thromboembolism occurring in the population, which are clearly not related to oral contraceptive usage or only slightly increased by its use, would tend to obscure a *true* association among otherwise idiopatic cases. Such effects require a still further increase in the size of study populations needed to detect such risk. The implications that follow-up studies of several thousand women can detect the rare risks implicated by retrospective studies of these conditions is a serious underestimation of the problem.

The article also deserves challenge with regard to an interpretation of biological mechanisms of disease since overemphasis is given to the importance of nonincreased thromboembolism risks in pregnancy (with studious avoidance of the puerperium). It is obvious that many important physiologic differences, e.g., hypervolemia, increased cardiac output, and increased secretion of cortisol and other hormones (including androgens), occur during pregnancy which do not occur during oral contraceptive usage. Because nature has carefully guarded her secrets as to why pregnant (but not puerperal) women are protected from increased thromboembolism does not mean that either no or trivial differences exist in such risk between pregnancy and oral contraceptive usage as the authors have implied.

More subtle and detailed explanations would be needed as to why selection of "idiopathic" thromboembolic disease is justified in the retrospective studies and why higher relative risks were found with idiopathic versus nonidiopathic disease. Although space limitations in this letter do not permit such discussion, these aspects need to be reviewed in order to represent fairly the careful retrospective studies designed to evaluate potential thromboembolism risks of oral contraceptive users who are mainly younger, healthy women. With the assumption that oral contraceptive usage may contribute to the risk of serious thromboembolic disease, it is scientifically important to study possible mechanisms rather than to disregard any relationship, since important understanding may be gained in relation to the natural disease.

Without prolonging this letter, in my opinion the generous space given to this article in your respected JOURNAL emphasizes a particular viewpoint which cannot be considered either a total overview or an accurate assessment of research performed on the question of risk of rare vascular events associated with oral contraceptive usage. Furthermore, the implications extend beyond the matter of estimating risk or nonrisk of oral contraceptive usage per se and relate to the total problem of clinical and population research strategy and design needed to detect uncommon and rare disease associations. An impartial review of these questions related to oral contraceptive usage is needed.

A. T. Masi, M.D., Dr.P.H.
Director, Division of Connective Tissue Diseases
Department of Medicine
University of Tennessee
858 Madison Avenue
Memphis, Tennessee 38163

To the Editors:

A recent paper by Goldzieher and Dozier[1] entitled "Oral contraceptives and thromboembolism: A reassessment," reviews the current literature regarding the influence of oral contraceptive use on the occurrence of thromboembolic events. Unfortunately, the value of this important undertaking is substantially limited by the authors' all too obvious biases. Their entire emphasis is on finding fault with studies reporting an association between oral contraceptive use and thromboembolism while ignoring the positive aspects of such

Table I. Age/race–adjusted estimates of the *relative risk of stroke* associated with the use of oral contraceptives

	Comparison with hospital control group				*Comparison with neighbor control group*			
	Thrombotic stroke		*Hemorrhagic stroke*		*Thrombotic stroke*		*Hemorrhagic stroke*	
	Relative risk	*95% Confidence limits*	*Relative risk*	*95% Confidence limits*	*Relative risk*	*95% Confidence limits*	*Relative risk*	*95% Confidence limits*
*A: Blood pressure**								
Normal†	3.3	1.5- 7.2	1.8	0.8-4.4				
Borderline hypertension	4.2	1.6-10.9	1.8	0.6-6.1				
Moderate hypertension	3.0	1.0- 9.0	1.5	0.5-4.5				
Severe hypertension	2.6	0.8- 8.8	1.2	0.4-3.6				
B: Cigarette smoking history								
Never regular	2.9	1.4- 6.0	1.2	0.5-3.0	3.2	1.6- 6.4	1.2	0.5-2.9
Once regular	7.5	2.4-23.3	2.5	0.8-7.7	3.9	1.3-11.7	1.5	0.5-4.4
Now regular (<1 pack/day)	3.4	1.2-10.2	1.7	0.6-4.8	4.2	1.5-12.1	2.1	0.8-5.6
Now regular (≥1 pack/day)	4.5	2.0-10.1	2.5	1.2-5.3	3.9	1.8- 8.7	2.3	1.1-4.7
C: Migraine history†								
No	4.4	2.5- 7.8	1.9	1.1-3.4	4.9	2.9- 8.3	2.2	1.3-3.6
Yes	4.1	1.9- 9.1	2.1	0.9-4.9	2.9	1.3- 6.4	1.3	0.6-3.0

*Source of data was hospital records so comparisons were possible only with hospital control subjects.
†See original manuscript for definition of terms.

studies. Furthermore, consistently throughout the manuscript they have referred to retrospective methods of study by the denigrating term of "trohoc" coined by Dr. Alvan Feinstein. This ignores the many thoughtful and experienced epidemiologists and statisticians who have used this method and find it, when properly used, a valuable epidemiologic tool. In many instances results from such studies have been validated by subsequent prospective studies.

It is impossible to address all of the misleading contentions and allegations made in the paper, and we will speak only regarding those issues raised with respect to the study conducted by the Collaborative Group for the Study of Stroke in Young Women, hereafter referred to as the collaborative study.[2, 3] In addition, we will comment briefly on the attempt made by the authors to relate the results of the collaborative study to the Mayo Clinic studies.[5, 6]

The collaborative study was a case-control study and is described well and accurately by Goldzieher and Dozier (p. 898). In addition to the data presented in the two publications emanating from this study,[2, 3] Dr. Goldzieher has had access to additional details made available to him at his request.

The authors' criticisms of the collaborative study may be summarized in three categories.

1. They claim that the findings are not homogeneous in that four of the 12 collaborating centers show a lower rate of oral contraceptive use in the stroke group than in one or both of the control groups.

2. They believe that there could be problems with the results of the interviews in that: (a) there was a high nonresponse rate, (b) some interviews were completed by surrogates when the woman involved was unable to respond, and (c) the interviewers were not blind to the clinical status of the person being interviewed, i.e., whether she was a case or a control subject.

3. They note differences between case and control subjects which apparently were not "adjusted for" in the analyses.

Responses to each of these criticisms follow in order.

1. From the very onset of the Collaborative Group study, its primary objective was to examine the possibility that oral contraceptive use might be related to the occurrence of *thrombotic stroke*. The original publication states this objective clearly and describes in detail the pains taken to assure the accuracy of the diagnoses.[2] Of the 182 diagnosed cases of thrombotic storke, 140 (77 per cent) had a completed interview, and these were related to the 120 and 138 completed interviews among the corresponding hospital and neighbor control subjects, respectively. These thrombotic cases showed a rate of oral contraceptive use which was higher than in either control group uniformly for all 12 of the collaborating centers. Thus, there is no basic inconsistency in the data from the four centers *if we restrict our attention to thrombotic strokes.*

Of the 152 interviewed stroke patients from the four centers referred to by Goldzieher and Dozier, 112 (73.7 per cent) were *not* categorized as thrombotic in contrast to 177 of 277 (63.9 per cent) in the remaining eight centers. This significant difference is entirely due to the fact that 28.9 per cent of interviewed stroke patients from the four centers were classified as "other" in contrast to only 18.1 per cent from the remaining eight centers. Although we have no explanation as to why this occurred, the fact that it did and the fact that there is no association of oral contraceptive use with "other" strokes in any of the centers offer a partial explanation why, when all strokes are taken as a whole, there is no

uniform excess of oral contraceptive use among the case subjects in contrast to the control group in these four centers.

Consequently, these four centers, providing 35.4 per cent of our interviewed stroke patients (not "nearly half" as stated by the authors), do differ from the remaining eight centers in some respects but *not* at all to the point of invalidating the study as a study of oral contraceptive use and thrombotic events.

2. There is a serious misstatement on p. 899 (first column, first new paragraph, first sentence) wherein the authors state that 64 per cent of the subjects were not interviewed. Indeed, the truth is that 64 per cent of the subjects *were interviewed personally* whereas another 9 per cent of the interviews were completed by a surrogate, for an over-all completion rate of 73 per cent.

Because stroke in these young women was often a fatal illness, it is not surprising that the need for a surrogate responder arose much more frequently among the case group than control subjects. Indeed, Dr. Goldzieher has been provided data showing that fully 1/3 of the interviews of case subjects were completed by a surrogate whereas only 2 per cent of the interviewed hospital control subjects and none of the neighbor control subjects required such a surrogate. As mentioned in their paper, if a responder could not give a detailed history of oral contraceptive use, the subject was declared a "nonuser" for purposes of analysis. Consequently, it is an absolute certainty that oral contraceptive use was actually underestimated in the cases. Even with this consideration, thrombotic patients were still found to have a significantly higher rate of such use than the control group. Goldzieher and Dozier, though aware of this fact, have consistently failed to acknowledge this and its consequences, in essence, that the use of surrogates diluted the observed relationship and that the implications of the study would undoubtedly be even stronger if surrogate respondents had not been necessary.

It is indeed true that the interviewers were not "blind" as to whether the subject being interviewed was a case or control subject. However, they had no way of knowing the type of stroke, i.e., thrombosis, hemorrhage, or other form of cerebrovascular disease. Since the relative risk for thrombotic, hemorrhagic or other types of stroke differed considerably, it is obvious that interviewer bias could not have been a factor. Moreover, the questions related to oral contraceptive use were quite detailed and information was related specifically to the date of the stroke which the interviewer did not know. There were more than a dozen interviewers used in the study, and it is extremely difficult to believe that each of them would have been biased in the same direction.

3. Goldzieher and Dozier also commented on differences between cases and neighborhood control subjects on four factors possibly related to oral contraceptive use. These data are summarized in the following table which corresponds to Table IX, p. 899, in their paper[2].

	Case subjects (%)	*Control subjects (%)*	*Correct analysis*		*Goldzieher Dozier analysis* χ^2
			χ^2	*p*	
Unmarried	29.3	23.1	4.4	$p < 0.05$	9.6
Income less than $7,000 per year	37.7	30.0	8.4	$p < 0.005$	17.0
Elementary education or less	15.5	11.4	3.3	$0.05 < p < 0.10$	8.0
Regular smoker	73.8	54.2	36.3	$p < 0.0001$	65.5

Two points need to be made about these data. The first is that the tests of significance proposed by Goldzieher and Dozier are incorrect. They have been performed under the erroneous assumption that the control group is not a sample from a larger population but actually is the population. The proper chi-square and "p" values are given in the above table, and it is clear that there is a substantial difference between this analysis and the results presented by Goldzieher and Dozier. Indeed, in one instance a difference claimed to be highly significant ($p < 0.005$) is not even significant ($p > 0.05$). It is certainly to be expected that all authors will seek out those statistical procedures which will yield the most powerful results. However, it behooves them to be especially careful that a search for such power does not blind them to the inappropriateness of the techniques employed. This would seem most especially required of authors who demand such a high level of statistical perfection in others.

The second point to be made regarding the authors' evaluation of these data is the fact that they ignored the implications of the observed differences. It is well known that the rate of oral contraceptive use is highest among women from a higher socioeconomic class and women with more education[4]; furthermore, it seems likely that it is higher among married than single women. In the collaborative study, however, it is the control group which contains more married women and more women with higher income and education and presumably, therefore, more oral contraceptive users. Despite this, that study showed consistently that the patients with thrombosis use oral contraceptives more frequently than do the control group. Goldzieher and Dozier do not comment on this although they are most certainly aware of the importance of such factors. As far as the smoking differences are concerned, this risk factor was reported extensively in the second publication of the collaborative study,[3] and it was demonstrated that the differences in oral contraceptive use

between case and control subjects were present in all smoking categories.

Thus, the authors' analyses of these differences between case and control subjects are statistically faulty and logically specious and serve only to obfuscate matters. This is not at all worthy of anyone espousing the scientific method.

Additional attempts at obfuscation are evident throughout their paper. For example, in their brief reference to the second publication of the collaborative study,[3] they italicize a statement about overlapping confidence limits and thus emphasize the fact in such a way as to suggest that some serious sin was committed. And yet this fact is precisely the cornerstone of several of the arguments made in that paper[3] and in *no way* reflects upon the association between oral contraceptive use and thrombotic strokes. The tables containing the confidence limits under question were presented as they were in order to reflect our efforts to determine whether there was an interrelationship between the effects of oral contraceptive use and the other risk factors being studied (high blood pressure, cigarette smoking, and migraine history). In an attempt to clarify matters, we present herein a table of relative risks associated solely with the use of oral contraceptives within given levels of the risk factors being studied (Table I). Parts A, B, and C of this table refer respectively to Tables 2, 3 and 4 from the original manuscript.[3] Perhaps the most notable aspect of this table is the remarkable consistency observed in the estimates of relative risk. Thus, the estimates of the relative risk of thrombotic stroke are essentially the same, no matter which control group is used or what level of the other risk factors is involved.

Finally, the authors claim that meaningful conclusions from this study are impossible and then give a reference apparently in support of their claim. Upon examination of this reference it is seen to be a "Letter to the Editor" of the *New England Journal of Medicine* from three individuals whose very own words condemn them as being ignorant of the very basic epidemiologic tools. The effect of this reference is to give this final condemnatory remark even more weight in the eye of the reader, although upon careful scrutiny it proves to be but another example of their specious arguments.

We will now close with some comments regarding the authors' reference to the careful studies carried out at the Mayo Clinic.[5, 6] The rates which they quote of 9.3 and 2.9 per 100,000 women per year for the periods 1955 to 1960 and 1961 to 1966, respectively, are based on six and two cases of thrombotic stroke, hardly a large enough collection of data upon which to base any strong statements of trend. They then attempt to relate the relative risk of 9 from the original publication of the collaborative study[2] to *all* strokes in the Mayo Clinic experience. There can be no excuse for this egregious error as they are perfectly aware that this relative risk only applied to thrombotic strokes. It is only another example of the lengths to which they go in an attempt to discredit that with which they disagree.

We have attempted herein to respond to what amounts to an irresponsible, biased attack on a study with which we were involved. We are not claiming that the study was perfect; however, neither was it valueless as these authors would have their readers believe. Besides the points which we have addressed, there are countless minor irritations which remain unanswered. The thoughtful reader will have to seek out the original manuscripts and review matters for himself as this article is so hopelessly biased as to be actively harmful.

W. M. O'Fallon, Ph.D.
Head, Section of Medical Research Statistics
Mayo Clinic
Rochester, Minnesota 55901

Albert Heyman, M.D.
Professor of Neurology
Duke University Medical Center
Durham, North Carolina 27710

A. M. Lillienfeld, M.D.
Professor of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University
Baltimore, Maryland 21205

REFERENCES

1. Goldzieher, J. W., and Dozier, T. S.: Oral contraceptives and thromboembolism: A reassessment, AM. J. OBSTET. GYNECOL. **123:** 878, 1975.
2. Collaborative Group for the Study of Stroke in Young Women: Oral contraception and increased risk of cerebral ischemia or thrombosis, N. Engl. J. Med. **288:** 871, 1973.
3. Collaborative Group for the Study of Stroke in Young Women: Oral contraceptives and stroke in young women, J. A. M. A. **231:** 718, 1975.
4. Ryder, N. B., and Westoff, C. F.: Use of oral contraception in the United States, 1965, Science **153:** 1199, 1966.
5. Schoenberg, B. S., Whisnant, J. P., Taylor, W. F., and Kempers, R. D.: Strokes in women of childbearing age. A population study, Neurology **20:** 181, 1970.
6. Matsumoto, N., Whisnant, J. P., Kurland, L. T., and Okazaki, H.: Natural history of stroke in Rochester, Minnesota, 1955 through 1969: An extension of a previous study, 1945 through 1954, Stroke **4:** 20, 1973.

To the Editors:

In response to the paper entitled "Oral contraceptives and thromboembolism: A reassessment" (AM. J. OBSTET. GYNECOL. 123: 878, 1975), I wish to correct some errors concerning the studies by Sartwell and associates and to comment on the more general issues.

The estimation of confidence limits on page 895 is invalid, because no estimate of the annual incidence of idiopathic thromboembolic disease (X) was made, or could be made, in this study. For one thing, cases occurring over a period of several years were included;

for another, there could not be a population base on which to calculate a rate; for still another, some cases were excluded because they could not be interviewed or because control subjects could not be found.

A simple and reasonably accurate way to estimate the confidence limits of the relative risk is the method proposed by Woolf. It rests on the estimation of the variance of the natural logarithm of the risk as the sum of the reciprocals of the four numbers in a 2 × 2 table. When the paired method of analysis is used, just the two disparate cells of the table may be taken. By this method, with the omission of those pairs in which the case was a student nurse, as the authors of the reassessment prefer to do, the results are as follows:

Method of analysis	*Relative risk*	*95% Confidence limits*	
		Lower	*Upper*
Unpaired	4.5	2.1	9.6
Paired	4.6	2.4	8.6

Only if the lower confidence limit were one or less would the risk be statistically insignificant.

The elaborate analysis on pages 896 and 897 of the effect of the difference in educational level on the relative risk is also spurious. It rests wholly on the assumption that "the relative risk is related to education." Why this assumption?

Fortunately, I have kept records since my retirement that permit a further examination of the data. The following table relates to the study group exclusive of all pairs in which one or both members was a student nurse, divided according to whether or not the educational attainment was beyond the high school level. Use of oral contraceptives within one month of admission is considered.

	Cases of thromboembolism			*Control subjects*		
		Users of oral contraceptives			*Users of oral contraceptives*	
Educational attainment	*No.*	*No.*	*%*	*No.*	*No.*	*%*
Beyond high school	77	35	45.5	59	11	18.6
High school or less	70	30	42.9	88	11	12.5
Total	147	65	44.2	147	22	15.0

In both groups, the difference in use of oral contraceptives between the better educated and less well educated women is quite insignificant. There is indeed a larger percentage of the more highly educated women in the case group, but this cannot explain the association of oral contraceptives with thromboembolism.

Another error on page 896 is the statement that we merely re-examined our data with just the student nurses excluded. We also reported, in both our papers, that an analysis was made with deletion of all pairs in which the case subject, her husband, her control subject, or the latter's husband had been employed just before the illness in a medical or hospital-related capacity. The relative risk for the remaining pairs was 7.5. Thus, the effect of including women in the "medically related" category was to reduce the risk, not to enhance it.

The senior author of the reassessment first published a criticism of our study in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in 1970, as he notes. The main focus of that attack was the disparity in estimates of the relative risk from the different cities in our study. This criticism is repeated in the reassessment; my reason for not discussing it in this letter is that at the time I made a published response, which I think—and he obviously does not—adequately disposed of that issue.

The reassessment places great emphasis on the fact that two prospective studies, one an experimental trial, failed to find a relationship between oral contraception and thromboembolism. One of these was the Australian study. This is only briefly described in the publication cited, in contrast to the great detail provided in the preliminary report of the British College of General Practitioners' study, which was of the same general nature. It was planned to have two control subjects per user, but the study ended with fewer control subjects than users. The initial number of subjects is not given, only the numbers seen at the end of the first and second years; the dropout rate in the second (and last) year was over 30 per cent. Twelve users and 50 control subjects gave a history of attacks of thromboembolic disease prior to recruitment. From the paper it appears that venous thrombosis occurrences during each study year were ascertained by querying the patients.

Nowhere is the number of superficial and deep venous thromboses given separately, but, as there were too few patients with "femoral, pulmonary, or arterial thromboses" for analysis, it is assumed that all or nearly all were thromboses of superficial veins only. Table 2 gives two sets of incidence figures for both users and controls in each year; I cannot understand these figures, but the incidence in the control subjects ranged from 3.1 to 5.2 per cent per year, which seems a remarkably high figure, although the author views it as low. The incidence of "venous veins" (presumably varicose veins) given in Table 2 was over 20 per cent in each year of the study! Can the author have meant prevalence? Finally, the British study is about thirty times as large as this one. For these reasons, among others, I cannot regard the Australian study as entitled to be weighed against the findings of the British Royal College of General Practitioners.

But it is this study of which the authors of the

reassessment say: "Thus, the long-awaited prospective survey which was supposed to confirm and authenticate the findings of the "trohoc" studies *failed to do so*" (the italics are those of the reassessment).

The Puerto Rico experimental trial is another matter. Such studies, if properly done, carry far more weight than observational studies. I have no doubt that this trial was initially well designed, with good randomization of subjects, but the follow-up procedures and findings are inadequately described. For one thing, nothing is said about the possibility that over an eight-year period some initial users of oral contraceptives might have switched to other methods, or abandoned contraception, and that some control subjects might have become users. Rates were based on the initial numbers of users and nonusers. If there were such crossovers, their effect would be to diminish any true difference between the experience of the two groups. No information is given as to whether the dropouts were evenly divided between users and nonusers or whether the cases initially called thrombosis and changed upon review to other conditions were reviewed blindly and were equally distributed between the two groups. Finally, and most important, the number of cases found was too small for firm conclusions to be drawn.

The unreliability of the retrospective method (dubbed "trohoc") is emphasized throughout the reassessment. This view is buttressed by reference to the opinion of a single authority. Most workers in epidemiology hold a different opinion. Numerous examples of associations first demonstrated by retrospective studies could be cited, and there have been few, if any, properly designed retrospective studies so tested which have not (Sartwell, P. E.: Retrospective studies: A review for the clinician; Ann. Intern. Med. 81: 381, 1974). The method has repeatedly proved itself reliable and useful, although unsuited for certain purposes.

The authors cite on page 897 a statement by Mantel and Haenszel concerning the nonrandom sampling of control individuals when matching is made on a number of factors. This did not prevent Mantel and Haenszel from proposing in the same paper a significance test which is very widely used today, nor does it inhibit the authors of the reassessment from testing the statistical significance of many of the observations which they question. Another quotation from the same paper by Mantel and Haenszel must have been overlooked by the authors, namely: "However, a mere catalogue of biases arising from the possibly unrepresentative nature of a sample of cases and controls should not *ipso facto* invalidate any study findings."

Many issues in the reassessment other than the strictly epidemiologic ones deserve comment, but I shall mention only two. In addition to numerous earlier ones, two recent studies have shown clearly that women using oral contraceptives have alterations in blood clotting mechanisms—those of Fisch and Freedman (Obstet. Gynecol. 116: 477, 1975) and Alkjaersig and associates (Am. J. Obstet. Gynecol. 112: 199, 1972). The reassessment discounts experimental evidence that administration of estrogens to male subjects enhances the risk of thromboembolism, on the very questionable grounds that findings in male subjects are irrelevant for female subjects.

Several groups, including our own, have published the results of retrospective studies which indicate that up to now, at least, oral contraceptives cannot be linked with breast neoplasms. It seems odd that the critics have not questioned these studies. Does this fact suggest a bias?

A reassessment done without bias (a word which, ironically, occurs often in the paper under discussion) would, I am confident, come to a different conclusion.

Philip E. Sartwell, M.D.

38 Cloutman Lane
Marblehead, Massachusetts 01945

To the Editors:

We are writing concerning the article by Drs. Goldzieher and Dozier entitled, "Oral contraceptives and thromboembolism: A reassessment," which appeared in the December 15, 1975, issue of the Journal.

We had a great deal of difficulty following the reasoning in the last paragraph of page 897, dealing with the differences in risk of thromboembolism between the idiopathic and nonidiopathic cases in our series. We would like to restate our explanation of these differences as we do not feel Drs. Goldzieher and Dozier dealt with it adequately.

> The markedly smaller risk as calculated from the whole case series, compared to that for idiopathic cases alone, is presumably due to a weakness of the control series. Ideally these women would be matched to the case series not only on demographic characteristics but also on the presence or absence of predisposing medical features; e.g., for a case with no predisposing factors the control would likewise have none, and for a case with a history of previous thrombosis the control would likewise have such a history. However, this was not feasible.
>
> The non-idiopathic cases have a much lower frequency of recent use of oral contraceptives than the idiopathics (22 per cent as compared to 57 per cent). The controls with predisposing factors would also be expected to have a lower frequency of use than the controls who lack predisposing factors, for the same reason, namely, the avoidance of this method of contraception by such women. Assuming, as seems reasonable, that the controls with predisposing factors are a small minority of all controls, the true relative risk for idiopathic cases would be slightly reduced and for non-idiopathic cases considerably increased.
>
> This explanation is supported by two British prospective studies now in progress. For example, in one of these studies fewer than one per cent of women with a prior history of thrombophlebitis chose oral contraception as

their method, while almost 11 per cent chose the intrauterine device. A similar shift was seen in women with varicose veins or coronary artery disease.

In order to assess the reasonableness of this explanation for the difference in risk between idiopathic and non-idiopathic cases, a sample of the cases of thromboembolism was reinterviewed a considerable period after their discharge from the hospital for the purpose of learning whether their physicians had reinstituted oral contraception. Had they done so, it would have been in disregard of the advice on the package insert that the method not be used by those who have sustained a prior thrombosis attack. Actually, of 31 previous oral contraceptive users among thrombosis patients who were queried after discharge, only one was found to have resumed this method. Among 65 women with thrombosis who had not used oral contraceptives within one month before hospitalization, again, only one was an oral contraceptive user after discharge from the hospital. These findings support the view that the non-idiopathic cases as a group are less likely to have the method prescribed for them than healthy women; hence, they would have a spuriously low relative risk compared to healthy women when studied by the case-control method, even though their 'true' risk might be as high as that of the idiopathic cases. They also provide heartening evidence that physicians are adhering to the current advice with respect to the contraindications for these agents.[1]

Also, on page 906, the authors stated that "no dose-related effect was demonstrated by this epidemiologic study." We actually concluded the opposite, i.e., that the risk of occurrence of thrombotic disease was related to oral contraceptive dosage.

Finally, their reference to our paper was incorrect and is as below.[1]

Paul D. Stolley, M.D.
Associate Professor
James A. Tonascia, Ph.D.
Associate Professor

Department of Epidemiology
The Johns Hopkins University
School of Hygiene and Public Health
615 North Wolfe Street
Baltimore, Maryland 21205

REFERENCES

1. Stolley, P. D., Tonascia, J. A., Tockman, M. S., et al.: Thrombosis with low-estrogen oral contraceptives, Am. J. Epidemiol. **102:** 197, 1975.

To the Editors:

Among the many errors and misrepresentations in the article by Goldzieher and Dozier (December 15, 1975, pages 378 to 914), three of those referring to our work are gross.

On page 894, in discussing two of the retrospective studies of the relationship between oral contraceptives and venous thrombosis which we[1, 2] carried out in the 1960's, Goldzieher and Dozier made the following statement: *"The incidence of oral contraceptive use in the control subjects is significantly different between the first and second samples* (italics theirs): 25 per cent of control subjects in the first study were users, against 8.6 per cent in the second control sample, a difference that is statistically significant (P = 0.01). The use of oral contraceptives certainly did not *decrease* (italics theirs) threefold in the time intervals examined."

Table I. Recurrence of thromboembolic disease in two groups of women in relation to previous history of thromboembolic disease and contraceptive choice (from Badaracco and Vessey[4])

Women by previous history of thromboembolic disease and subsequent recurrence	*No. of women at time of index admission*		
	Oral contraceptive users	*Nonusers*	*P*
No. without previous history	30	25	
No. with subsequent recurrences	3 (10%)	10 (40%)	<0.05
No. with previous history	12	17	
No. with subsequent recurrences	2 (17%)	9 (53%)	>0.1

In fact, in the first study, which covered the years 1964 to 1966, we found that 10 of 116 control women (8.6 per cent) used oral contraceptives while in the second study, which covered the year 1967, we found that 13 of 52 control women (25 per cent) did so. In view of the small size of both samples and the fact that the sales of oral contraceptives more than trebled[3] in the United Kingdom from 1964 to 1967, these data are eminently reasonable. Goldzieher and Dozier have evidently interchanged the control data from the two studies.

On page 901, Goldzieher and Dozier present the data shown in Table I, but without the percentages, which have been added by us. In their discussion of this table, they stated, "In the subjects *with a previous history* (italics theirs) of thromboembolic disease, the frequency of recurrence was the same in the former users and in the nonusers . . . . Quite another situation was observed in those *with no previous history* (italics theirs) of thrombophlebitis . . . . those who were *nonusers* (italics theirs) at the time of their first attack had a significantly *higher* (italics theirs) recurrence rate than those who had been users at the time of their first attack . . . ." Inspection of the percentages in the table indicates how misleading these comments by Goldzieher and Dozier are. The fact that one of the differences is "statistically significant" while the other is not does not detract from the over-all conclusion that the data for those with and without a past history of thromboembolic disease are *remarkably similar.*

Also on page 901, Goldzieher and Dozier start a discussion of "precipitating factors" by stating: "Since thromboembolism is basically a recurrent disease, one would suspect that a precipitating or augmenting factor (such as the oral contraceptives are hypothesized to

be) would increase the incidence of recurrence. Data available in the British studies fail to support this notion (Table XI)." Where do the numbers in their Table XI come from and what do they mean? Even as the authors of the two reports cited in Table XI, it took us some time to find out. In fact, of the 58 women with venous thromboembolism included in the first report,[1] 21 gave a history of *previous* thromboembolism. Of these 21, nine (43 per cent) were users of oral contraceptives and 12 (57 per cent) were not. Similarly, of the 26 women with venous thromboembolism included in the second report,[2] eight gave a history of *previous* thromboembolism, of whom three (37 per cent) were users of oral contraceptives and five (63 per cent) were not. Therefore, the data refer to the women's past history and provide no information whatsoever about the "recurrence of thromboembolism as related to oral contraceptive use."

An interim report of the findings in our large prospective study of women using oral contraceptives, which has been in progress since 1968,[5] will be published shortly.[6] So far as thromboembolic disease is concerned, the results conform closely with those obtained in the retrospective studies.

M. P. Vessey, M.A., M.D., F.F.C.M.
Professor of Social and Community Medicine
Sir Richard Doll, D.M., F.R.C.P., F.R.S.
Regius Professor of Medicine

Oxford University
8 Keble Road
Oxford OX1 3QN, England

REFERENCES

1. Vessey, M. P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromboembolic disease, Br. Med. J. **2:** 199, 1968.
2. Vessey, M. P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report, Br. Med. J. **2:** 651, 1969.
3. Vessey, M. P., and Inman, W. H. W.: Speculations about mortality trends from venous thromboembolic disease in England and Wales and their relation to the pattern of oral contraceptive usage, J. Obstet. Gynaecol. Br. Common. **80:** 562, 1973.
4. Badaracco, M. A., and Vessey, M. P.: Recurrence of venous thromboembolic disease and use of oral contraceptives, Br. Med. J. **1:** 215, 1974.
5. Vessey, M. P., Johnson, B., and Donnelly, J.: Reliability of reporting by women taking part in a prospective contraceptive study, Br. J. Prev. Soc. Med. **28:** 104, 1974.
6. Vessey, M. P., Doll, R., Peto. R., Johnson, B., and Wiggins, P.: A long-term follow-up study of women using different methods of contraception. An interim report, J. Biosoc. Sci. **8:** 1976. In press.

Reply

To the Editors:

Comment on letter by Dr. C. R. Kay. We respectfully suggest that Dr. Kay contain his outrage, for his categorical denial that "there is no arithmetical error in any of our tabulations" is simply not true. Kay confuses the situation by describing his use of more rigorous definitions of predisposing causes. This is not the issue. Kay's original denominators contain exposures of women with conditions that preclude their being classifiable as cases of first attack of idiopathic thrombosis. This is a basic impropriety in epidemiology, as discussed, for example, by B. MacMahon and T. F. Pugh (Epidemiology, Principles and Methods, Boston, 1970, Little, Brown & Company, p. 70). Simply put, women with predisposing conditions cannot, by definition, contract idiopathic disease.

The recalculations published by Kay, in 1975, were not, in fact, figures to correct the errors in the original 1974 report. They apparently pertain to expanded data with the exclusion of predisposed and pregnant women from both the numerator and the denominator. We still have no idea what the original rates or ratios of rates would have been when correctly calculated. For comparison, we do not know what the updated calculations would have been if done the old way. What Kay has given us instead is a comparison of original data calculated incorrectly with expanded data calculated correctly. This is hardly the resolution of doubt that Kay purports to have provided. Perhaps this will be revealed in the "full report" he has twice promised (Lancet 1: 1381, 1975; J. R. Coll. Gen. Pract. 25: 904, 1975).

The use of "standardized" rates or of age/race-adjusted values (as in the Heyman study on strokes) is a proper way of trying to compensate for differences in populations subjected to epidemiologic surveys. The magnitude of the changes (or the lack thereof, as in the present instance) which can be brought about by such adjustments is disquieting. In the letter of O'Fallon and associates, we find that such an adjustment can lower a relative risk from 13.6 to 2.6; they had previously adjusted certain published relative risks of 8.8 and 9.5 down to 4.1 and 4.4. Such flexibility, achieved entirely within allowable epidemiologic manipulation, does not increase confidence in the reality of the computed values.

Comment on letter by Dr. A. T. Masi. Dr. Masi's comments regarding the Sartwell and Vessey-Doll papers are taken up elsewhere in our commentary. His discussion regarding sample size in prospective studies is quite confused. First, he carefully obfuscates the fundamental difference between prospective clinical observations (such as the studies of the Royal College of General Practitioners and the Australian College of General Practitioners) where users and nonusers are self-selected (with the attendant bias) and clinical *experiments* (such as the Fuertes-de la Haba study) where users and nonusers are assigned by properly randomized design. (The statement that a 10,000 patient *experiment* is "small-scale" is rather amusing.) Then he proposes zero occurrences in a theoretical control group and proceeds to calculate the chi-square value. That this is improper is widely recognized by statisti-

cians: Fisher's exact test is customarily employed instead (see Maxwell, A. E.: Analysing Qualitative Data, New York, 1961, John Wiley & Sons, Inc., p. 23; Armitage, P.: Statistical Methods in Medical Research, New York, 1971, John Wiley & Sons, Inc., pp. 135-138). While the chi-square calculation may be used for his second example of 40 occurrences, Masi does not make Yates' correction for continuity (see Maxwell, *loc. cit.;* Armitage, *op. cit.,* pp. 134-135; Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Methods for Rates, and Rates and Proportions, New York, 1973, John Wiley & Sons, Inc., pp. 19-20). All these obfuscations and errors aside, Masi makes a very important point: that *idiopathic* cases (whose incidence is allegedly increased by oral contraceptive use) form a very small fraction of the totality of thromboembolism cases in the United States. "Trohoc" studies have repeatedly shown that the "relative risk of oral contraceptive use" is negligibly small when *all* cases, rather than *idiopathic* cases, are examined. Therefore, it is entirely correct to point out that an increase in disease incidence in the small number of idiopathic cases might be buried in the large number of nonidiopathic, low-incidence cases. The argument proposed by Drs. Stolley and Tonascia in their letter, purporting to explain the low incidence of thromboembolic disease in predisposed cases, seems however to vitiate Dr. Masi's point. Stolley and Tonascia explain the low incidence in the predisposed group as the result of underprescribing of oral contraceptives to such subjects by their physicians. In the Puerto Rico experiment, there was no underprescribing—since the subjects were randomly assigned to hormonal or nonhormonal contraceptives—and, therefore, the incidence of thromboembolic disease ought to be at least as high, or higher, in the predisposed cases as in the idiopathic cases. Thus, there would be no mass of low-incidence cases in which the high-incidence idiopathic cases could get lost. In any event, this argument is academic, for Dr. Fuertes has informed us, in a reply generated by Dr. Masi's and Dr. Sartwell's letters, that cases with predisposition were excluded from enrollment.

The identification by Dr. Masi of myocardial infarction as one of the "rare, serious thromboembolic events occurring in otherwise healthy women using oral contraceptives" deserves special mention. This is an obvious reference to the publications of Mann and associates (Br. Med. J. 2: 241 and 245, 1975), which patently did *not* involve "otherwise healthy women." In fact, in Mann's morbidity study, there was only *one case subject* who was a user and who did not also have one of Mann's designated risk factors.

We wish to commend Dr. Masi for his consideration of the biological mechanisms of disease vis-à-vis the pregnant state. However, we in no way stated that there were "no trivial differences" between oral contraceptive users and pregnant women, as he suggests. We emphasized the low incidence of thromboembolism in pregnancy "because of the intense exposure to estrogens and progestins that accompanies pregnancy and because of the increase in coagulation factors and decrease in fibrinolytic factors that exist to a much greater degree than during oral contraceptive use" (p. 884). If Dr. Masi can tell us how "hypervolemia, increased cardiac output, increased secretion of cortisol and other hormones (including androgens)" can nullify the clinical consequences of the so-called hypercoagulable state, he will have made a major contribution to our knowledge of hemocoagulation. Until then, a mere enumeration of the physiologic differences between pregnancy and oral contraceptive use in no way explains the glaring inconsistency to which we have called attention. The reasons for our "studious avoidance" of the puerperium should be obvious to obstetricians, if not to epidemiologists; the role in thrombophlebitis of the stresses of labor, prompt ambulation, and other factors in the postpartum state which have no parallel in oral contraceptive users are so well known, we thought, as to deserve no comment.

Comment on letter by Drs. O'Fallon, Heyman, and Lilienfeld. We are in full agreement with O'Fallon and colleagues that the "trohoc" method is, "*when properly used* (italics ours) a valuable epidemiologic tool. In many instances, results from such studies have been validated by subsequent prospective studies." Repeatedly, in our paper, we stressed that the "trohoc" method, despite its flaws, is useful as a "fishing expedition" and that our criticisms were directed at misuse, misinterpretation or misextrapolation of this method. It is true that "many instances" have been in agreement with subsequent prospective studies; in other cases, of course, they have not. The fact that there is disagreement with the one clinical *experiment* that has been carried out is glossed over as usual.

The statement that "from the very onset . . . the primary objective (of the Collaborative Group study) was to examine . . . that oral contraceptive use might be related to the occurrence of *thrombotic* stroke" is certainly not apparent from the original publication (see, for example, the opening sentences of the abstract of this paper: "A case-control study was conducted to determine the relation between the use of oral contraceptives and the occurrence of stroke in young women") or from the series of newsletters sent to participants. Perhaps this emphasis arose *post hoc,* after the data were analyzed.

The authors did not originally publish in 1973 or 1975, do not at this time reveal, and did not supply us personally with the critical distribution of thrombotic cases among the 12 cities. In the 1973 paper, emphasis is given to *total cases* (thrombotic, hemorrhagic, plus other), compared to hospital and neighbor control subjects, as they relate to the percentage thereof who were classified as users. In response to our request of October 3, 1973, for the actual numbers involved, Dr. Heyman kindly supplied these in his answer of October

31, 1973. The classification was for *total cases* of stroke. On March 25, 1975, we requested the racial breakdown by city and received this tabulation, on April 22, 1975, for *total cases*. Thus, the only place where thrombotic strokes are separately described for the four deviant cities is in Table 3 of the 1973 paper, where the figures are given for the four cities *combined*, as contrasted to the total of 12 cities (which includes the four deviant cities). Therefore, we have never seen any evidence that the use rate was "uniformly" higher for patients with thrombosis than for either control group, as is now stated for the first time by O'Fallon and colleagues.

The criticism in the final paragraph of their category (1) serves as an example of the strawman technique. The letter states, " . . . these four center, providing 35.4 per cent of our *interviewed* stroke cases (not 'nearly half' as stated by the authors)." Contrast this with what we *actually* stated on page 899: " . . . *the four cities that provided nearly half (42 per cent) of the* ***eligible*** *cases of stroke included in the entire study.*" The tabulations provided us on April 22, 1975 revealed 45 *eligible* total cases in Atlanta, 136 in Baltimore, 49 in Detroit, and 18 in Cleveland. These numbers add up to 248, which is easily calculated to be 41.5 per cent of the 598 *eligible* cases. It was only necessary for them to change one word in order to suggest that an error had been made.

The authors are correct in calling to our attention the fact that the word "not" should not appear in the sentence cited on page 899 of our paper.

In any public opinion survey, there is always a third category of responses such as "no opinion" or "I don't remember." It is significant that not a single "trohoc" publication on oral contraceptives presents such a categorization. In the present instance, such responses were classed as "nonusers," although the published reports do not reveal this. The argument by the authors *assumes* that such responses were restricted to the surrogates. With consideration of the neighborhood control subjects, which contained no surrogate responses, this group above all would be expected to have the highest frequency of "I don't remember" responses, for the simple reason that they had no identifying hospitalization date to relate to the index date. Since these would presumably be classified as "nonusers," the calculated frequency of oral contraceptive use would be artificially decreased and the relative risk derived therefrom would be artificially increased, thus offsetting the error in the "case" classification to an indeterminate degree.

We stated (p. 899) that, ". . . data on oral contraceptive use were not obtained in a 'blind' fashion—one of the prime requisites for avoiding bias." This is a basic epidemiologic consideration (MacMahon, B., and Pugh, T. F.: Epidemiology. Principles and Methods, Boston, 1970, Little, Brown, & Company, pp. 257-258). However, the authors tell us that, "it is obvious that interviewer bias could not have been a factor" because they had "no way of knowing the type of stroke." This is really irrelevant, as they certainly had sufficient and adequate means of knowing whether the respondent was a case or a control subject. It is difficult to envisage otherwise, most particularly so in the situations where the stroke was lethal and a surrogate was the respondent (true for "fully ⅓ of the interviews of cases" we are advised).

In contrast to the authors, we do not find it "extremely difficult to believe that each (of the interviewers) would have been biased in the same direction." Considering the alarmism which has been propagated by the media for years and the rumors which have circulated regarding the interviewers used in some studies, we feel that concern about interviewer bias is entirely legitimate. There is also no need to suppose that interviewer bias had to affect all types of stroke precisely to the same degree; random differences in the degree of bias might well have occurred and affected the groups differently. The methodologic problems inherent in any interview study are well known to pollsters, psychologists, and others involved in these techniques, and elaborate systems have been incorporated into such investigations to test for adequacy of the testing technology, the absence of bias, etc. Space limitations have undoubtedly prevented the "trohoc" investigators from providing the details requisite to assure others that these tests have been made and met. In the absence of such proof, careful scientists cannot be faulted for suspending acceptance.

The authors have supplied corrected chi-square values in our Table IX. There was clearly a computational error, and we thank them for the correction. However, the "substantial difference" which this is claimed to make turns out, in fact, to be that *one* of the four differences between case and control subjects no longer reaches the accepted level of statistical significance.

The second point discussed is education and marital status; the authors state that " . . . it is the control group which contains more married women and women with high income and education." More than what? Fig. 2 in their publication reveals that the comparison is more than all cases, i.e., thrombotic, hemorrhagic, and other, combined. Their letter then makes the following quantum jump: "Despite this, that study showed consistently that the thrombotic case subjects use oral contraceptives more frequently than the control subjects." The argument from *all* cases to thrombotic cases *only* cannot be accepted, since they consider this an "egregious error" when used by us.

With regard to smoking differences, the writers did report, in their 1975 paper, differences in oral contraceptive use between case and control subjects for all smoking categories. What they neglect to tell the readers of their present letter is that there were *overlapping confidence limits* in each of the 16 comparisons except for the thrombotic case subjects regularly smoking more than one pack of cigarettes a day (their Table 3).

Table I. Distribution of relative risk

Relative risk	*No.*	*In class (%)*
0-0.9	18	7
1-1.9	71	28
2-2.9	30	12
3-3.9	24	10
4-4.9	*23*	*9*
5-5.9	3	1
6-6.9	11	4
7-7.9	9	4
8-8.9	9	4
9-9.9	0	0
>10	52	21
Total	250	100

Even here, the limits nearly adjoin: 1.8 and 1.9; 2.6 and 2.9. We discussed this on page 900 of our reassessment.

The new and rather confusing table provided by the Committee and some data in their second publication deserve comment. In that second publication, they recalculated their original estimates of relative risk by ignoring matching and using instead an age/race stratification. This procedure, as they pointed out, reduced their original values of relative risk from 8.8 and 9.5 (neighbor and hospital control subjects, respectively) to 4.1 and 4.4—a substantial difference. We are now provided with a new age/race–adjusted recalculation of Table 2 of that second paper. The original relative risks (by degree of hypertension and for thrombotic strokes only) are now changed from 3.1, 5.2, 8.9, and 13.6 down to 3.3, 4.2, 3.0, and 2.6—another remarkable decline in the calculated relative risks. This makes it quite clear that relative risk calculations are highly susceptible to various (legitimate) arrangements of the data. Table 2 of the second publication permitted a comparison of the confidence limits of the relative risk for users versus those of the nonusers. As we pointed out in our publication, these overlapped in every instance. With the new calculations, which so dramatically reduce the relative risks in the hypertension groups, it is even more likely (although the authors fail to provide the calculation) that the confidence limits of the relative risk between users and nonusers will still overlap.

The authors' remarks concerning our comparison of their prognostications with the data of the Mayo study simply obfuscate the issue by ignoring what we said regarding thrombotic strokes. They take exception to our calculation for *all* strokes (analogous to one they themselves made) but make no mention of the fact that our calculation for thrombotic strokes is equally incompatible with their estimates of relative risk. The objection that calculations from the Mayo study are based on small numbers should apply both ways: the "trohocers" have no hesitation about fourfold tables with very small numbers (Table 2 of their second paper contains six cells with less than eight subjects), but apparently such usage is not permissible to holders of different views.

Comment on letter by Dr. Sartwell. The first of Dr. Sartwell's gentlemanly comments is quite valid. Our estimate of the annual incidence of idiopathic thromboembolic disease was based on the data of Vessey and Doll, and, as Sartwell avers, this may not be appropriate to the population studied by his group.

Dr. Sartwell proposes the use of Woolf's method (Biometrics 21: 86, 1965) for calculating the confidence limits of the relative risk and states, "Only if the lower confidence limit were one or less would the risk be statistically insignificant." In fact, with this method of analysis, and Sartwell's relative risk of 4.5, and No. = 67, it is a *mathematical impossibility* for the relative risk to be unity or less. The relative risk would have to be 1.577 or less for it to be *possible* to have a lower confidence limit ≤ 1. We have performed a further examination of this relative risk in the following way: With the sum of the deviant cells taken to be 67, we instructed the computer to calculate 250 random partitions and compute the relative risk as the larger number divided by the smaller number in each partition. The distribution is as shown in Table I.

The distribution reveals that only risks greater than 5 and less than 9.9 could be expected in less than 5 per cent of the 250 random partitions. This shows that risks of the order of 4.5 (as calculated by Sartwell) could be expected to occur *randomly* as much as 9 per cent of the time (compared to 5 per cent or less which is taken as the usual level of significance).

When relative risk was calculated by Sartwell with the exclusion of medical or medically related subjects, the relative risk for the nonmedical group was 7.5, and that for the medically related group was 3.0. It is difficult to understand why the medical group would demonstrate a risk two and one-half times *less* than that of the nonmedical subjects, since by Sartwell's own admission this group " . . . probably indicates a greater likelihood of employees receiving medical attention and being admitted to a teaching hospital if they develop this type of illness while working."

Our analysis on pages 896 and 897 is indeed given "with the assumption that the relative risk is related to education." Sartwell asks, "Why this assumption?" If one refers to page 199 of his second paper (Am. J. Epidemiol. 94: 192, 1971), one finds: "Using a dichotomous classification, I have divided the material into those pairs who were alike on education and those who were dissimilar pairs. As Table 9 shows, the pairs that were dissimilar on this factor yield a much higher estimate of risk." Sartwell's Table 9 shows the dichotomous risk estimates for *similar* educational levels to be 35/11 or 3.18 and that for *different* educational levels to be 22/2 or 11.0. Thus, one observes a 3.4-fold difference.

The new tabulation provided by Sartwell allows one

to calculate a relative risk for the more educated of 3.8 versus that for the less educated of 5.2, a 1.4-fold difference. Sartwell deems this "quite insignificant." Further, it is stated that the admitted excess of better educated women in the case group "cannot explain the association of oral contraceptives with thromboembolism." One need not be overly imaginative to propose that it is the very element of education, and attendant intelligence and greater breadth of reading, that allows an individual to make the association between the use of oral contraceptives and her symptoms of possible thromboembolic disease. This is the lay equivalent of the "index of suspicion" thesis propounded by Hougie (Am. Heart J. 85: 538, 1973).

Sartwell's new tabulation pertains to "the study group exclusive of all pairs in which one or both members was a student nurse." He shows 147 such cases; however, his original paper showed 149 and the missing two cases go unexplained. The original paper further stated (p. 371) that, when the student nurses were excluded, "The difference in educational level and the difference in proportions working outside the home were found to be no longer statistically significant, but the difference in the proportion employed in a medically-related position remained." It is stated by Sartwell that, "We also reported, *in both our papers*" (italics added) on analyses excluding all cases involving medically related employment. As a matter of fact, Sartwell's original 1969 paper is devoid of such analysis, which he plainly admits in his 1971 paper on pages 197 and 198: "The second, more drastic, was to delete all pairs in which either member had any sort of medically-connected job. The results of this analysis, *which were not given in the previous paper,* are shown in Table 7" (italics added). Sartwell's Table 7 displayed 92 pairs *with* a medically related job. This should be contrasted with the 77 case subjects and 36 control subjects with medically related jobs in Table 5 of the original 1969 publication.

In truth, Sartwell has never adequately disposed of the problem of widely differing risks in different cities. We quoted on page 897 his statement that the small samples had very large confidence limits. However, the excuse given for deliberately lumping such disparate findings in order to obtain one over-all figure was: "After all, the reason for having to collect data from five areas was to secure numbers sufficient to be meaningful" (Sartwell, *op. cit.*, 1971, p. 198). Such obscurantism was followed in subsequent "trohockian" exercises by others (e.g., Heyman, Stolley).

It will certainly not be argued that the British Royal College study was much larger and more detailed than that of the Australian Royal College. We called attention to the high incidence of thromboembolic disease on page 907 of our paper, remarking that this was "presumably the result of physician awareness."

Sartwell would appear to agree with us concerning the importance of the Puerto Rican experimental trial, even though he raises some *theoretical* questions concerning its conduct. Responses by Dr. Fuertes-de la Haba to the questions raised in the Sartwell letter are as follows: (1) There were no crossovers; (2) dropouts were almost equally divided between the two groups; (3) the internist who examined the patients did *not* know whether they belonged to the oral contraceptive or non–oral contraceptive group. The question of idiopathic versus predisposed cases is discussed in our reply to Dr. Masi. Sartwell considers most important that "the number of cases found was too small for firm conclusions to be drawn." If by "firm conclusions" he means the ability to prove the negative, then we agree that the Puerto Ricans, like everyone else in history, have not been able to do this. In any event, Sartwell does not contest the fact that the Puerto Rican studies were sufficiently large to detect "a relative risk of 3.0 or more with a 99 per cent certainty" (p. 910), which encompasses Sartwell's over-all relative risk of 4.4.

It is not true that the unreliability of "trohockery" is emphasized throughout our paper, as alleged by Sartwell. The point we thought we already made (p. 890) was that, "The real problem is that the 'trohoc' studies have been *misused* (italics added) by the experts . . . , misinterpreted by the policy-makers . . . , misunderstood by the general body of practicing physicians, . . ." etc. The argument that our "view is buttressed by . . . the opinion of a single authority (while) most workers in epidemiology hold a different opinion" would bring a reminiscent smile to the lips of Galileo, Pasteur, and others. Scientific truths, as far as we are aware, are not established by majority vote.

While Sartwell can aver that numerous examples of association were first shown by "trohockery," this is qualified by the words "properly designed" and "although unsuited for certain purposes." One of the earliest errors came from Sartwell's own department and was in fact cited in his 1974 review to which he now makes reference: the negative association between cancer and tuberculosis (Pearl, R.: Am. J. Hygiene 9: 97, 1929). In recent memory, we recall the examples of coffee and myocardial infarction, reserpine and breast cancer, meclozine and birth defects. (Sartwell also refers to Dorn's lecture at Harvard [N. Engl. J. Med. 261: 571, 1959], which is "must" reading for anyone contemplating the mysteries of "trohockery.")

The final issues raised by Sartwell must be dealt with briefly. Papers on coagulation factors and oral contraceptives are exceedingly numerous, and the two recent ones mentioned by Sartwell contribute nothing really new. The controversy of estrogens and thromboembolism in male subjects was not subjected to critical review in our reassessment. A careful reading of the pertinent papers concerning male subjects given estrogens following prostatic cancer, myocardial infarction, or stroke reveals contradictory results and only contributes to the confusion engendered by the literature on female subjects. To an endocrinologist, the notion

that estrogens can have qualitatively and quantitatively different effects in male as compared to female subjects is not questionable. There is a very large body of literature on this subject, to which Dr. Sartwell is referred.

"Trohockian" reports of decreased relative risk of oral contraceptive use associated with breast disease, though supported by prospective surveys, no more prove a *protective* relationship than the "trohockian" studies on thrombosis prove causation. The only bias in our not discussing these papers is the restriction we placed upon ourselves in the title of our article.

Comment on letter by Stolley and Tonascia. At the time our manuscript was prepared, we were in possession of only the typed draft by Stolley and associates, which was headed, "Submitted for publication to the *New England Journal of Medicine*, November, 1974." As it turned out, this journal did not publish the paper, and it eventually appeared in an epidemiology journal, as cited by Stolley and Tonascia. The draft manuscript was not identical in respect to the paragraphs cited in the present letter.

It is difficult to comment fully on the paper of Stolley and associates because their data were consistently displayed as either (a) all cases or (b) idiopathic cases. Nowhere is there an analysis of the difference, namely, (c) the nonidiopathic cases. The proper comparison, then, is not between the idiopathic cases and the total cases (which include all of the former), but the idiopathic and the nonidiopathic (whose sum equals total cases). This was not done in the paper, as Tables 3, 4, 5, 6, and 7 offer only the improper comparison.

The data provided in the letter of Stolley and Tonascia regarding the frequency of oral contraceptive use in idiopathic versus predisposed cases (57 versus 22 per cent) is of great significance. They state quite correctly that idiopathic case subjects should be compared with "idiopathic control subjects" (i.e., control subjects without predisposing factors) and predisposed case subjects should be compared with predisposed control subjects to eliminate the obvious bias in the frequency of oral contraceptive pill use. We wonder why such an analysis was "not feasible". In any event, this large difference in contraceptive habits raises the question whether studies such as that of Stolley and associates and Heyman and colleagues (in contrast to Sartwell, who used screened "idiopathic" control subjects) have any meaning whatever, since the two types of case and control subjects have very different oral contraceptive–use characteristics. The contention that "control subjects with predisposing factors are a small minority of all control subjects" needs to be documented and is in any event highly dependent on what set of predisposing factors are used to define the groups.

Their Table 7 and the paragraph entitled "relationship to dosage" on page 205 belie the conclusion that the "risk of occurrence of thrombotic disease was related to oral contraceptive dosage." Even if one ignores the different kinds of estrogens and progestins involved, the authors are only able to state: "For all cases, the larger dose carries only a slightly higher risk; for idiopathic cases the risk is approximately doubled with the larger estrogen content, but, as is evident from Table 7, *the confidence limits of the risk estimates overlap considerably*" (italics ours). We commented earlier on the predilection of "trohockians" to gloss over their findings on nonidiopathic cases. If Stolley's Table 7 is completed, by subtraction, to reveal the data for the nonidiopathic cases, it is discovered that neither estrogen group has a significant relative risk. In fact, the risk for the high-estrogen group turns out to be less. We wonder why this information was not revealed.

Comment on letter by Drs. Vessey and Doll. Drs. Vessey and Doll are correct in pointing out that the numbers describing control use of oral contraceptives in the two studies were inadvertently reversed in our paper. However, the conclusion that the incidence of use was significantly different in the two samples is not challenged by Vessey and Doll. Rather, they deem the difference "eminently reasonable," citing more than trebled sales in the United Kingdom, supposedly documented by a 1973 paper by Vessey and Inman (J. Obstet. Gynaecol. Br. Commonw. 80: 562, 1973). Inspection of Figure 1 in this paper reveals that, given a host of assumptions in the legend concerning personal communications from IMS Ltd. and FPA on sales figures, the authors depicted estimated sales in England and Wales (*not* in the United Kingdom, as alleged) as shown in the following table.

Year	*Thousand woman years*
1964	210
1965	370
1966	560
Average, 1964-1966	380
1967	760

The ratio 760/380 equals 2.0, which is quite different from "more than trebled," as claimed in the Vessey-Doll letter; and different from the 2.9-fold difference in the use figures of their control samples. We witness here the situation where one quotes incorrectly from one's own paper, which, in turn, is based upon assumptions based, in turn, upon personal communications. We cannot agree that this procedure, or the misleading and erroneous conclusion derived therefrom, is "eminently reasonable."

The second objection of Vessey and Doll refers to our Table X on page 901. They apparently missed completely the point that we were attempting to make, namely, that among the group not predisposed by virtue of prior thrombosis the recurrence rate was significantly higher for nonusers. Since this was not the case among those *having* a prior history, we raised the question as to whether ". . . the 'trohoc' studies might

be pointing to a spurious relationship resulting from the presence of two populations in one instance (those not predisposed by prior occurrence) and might be correctly indicating in the other instance (those so predisposed) the absence of an association when populations with a homogeneous past history and prognosis are being compared."

Instead of addressing themselves to the important generality that "trohoc" studies consistently find an association between thrombosis and use of the oral contraceptive pill only when idiopathic cases are considered, Vessey and Doll call our attention to the percentages 10 and 17, or 40 and 53, which they consider "remarkably similar." They have an undeniable right to make that judgment and to ignore statistical tests of significance on small numbers, which, on the other hand, are the lifeblood of "trohockery."

The third objection of Vessey and Doll relates to our Table XI on page 902. We take heart in the revelation that the authors find the data in the cited papers as obfuscated as we did. Apparently here, too, they miss the point. "Recurrence" of thromboembolism in a group of "cases" can only refer to *previous* thromboembolism. Certainly we were not speaking of attacks in the future! Contrary to providing "no information" as alleged, Table XI clearly demonstrates that the incidence of recurrence, based upon thrombosis *previous* to the present hospitalization, was not greater among users of oral contraceptives.

We look forward to the report of Vessey's large prospective study. In the meantime, however, we cannot accord any more substance to his "in press" reference in which the results "conform closely" than we could to his incorrect reference to personal communications in his 1973 publication.

Concluding remarks. A few general concluding remarks seem appropriate. The defamatory tone of many of the letters is worthy of note. If there were any doubts in the minds of onlookers that the proponents of the "pills cause clots" theory are emotionally involved in their position, these doubts must now be forever dispelled and the implications thereof taken into account in evaluation of their contributions. Hopefully the plentiful expressions of annoyance have served psychotherapeutically to ventilate some of these emotions so that future debate can be carried out in a more objective vein.

The respondents have understandably concentrated on rebutting criticisms of their own contributions; unfortunately they have addressed themselves only minimally to the larger issues we have tried to bring out. The intrinsic flaws in the case-control method have been answered by recourse to the argument that the prognostications are confirmed by prospective surveys "in many cases"; it follows, of course, that in other cases, they are not. Clinical experiments to the contrary are simply ignored or dismissed with essentially trivial arguments, and vital statistics which, as others have pointed out, are wholly unreliable (see J. A. M. A. 234: 605, 1975) continue to be used (Sartwell and associates: Prev. Med. 5: 15, 1976) to buttress their inferences. Also, the reverse side of the coin—the false negative—is not examined, for it is not often that a clinical experiment or a prospective survey would be undertaken to test the *lack* of an association. Thus, the true accuracy of the case-control method is quite unknown. On the other hand, what is certain is that the method is fraught with pitfalls of hypothesis and logic, hidden assumptions, technologic problems, undefinable data sets, and unperceived biases. Even if these can be minimized by skilled and objective investigators, the use to which the derived associations are put becomes perhaps the most objectionable feature of this epidemiologic device. We elaborated on this point in our paper, although the extensive current misuse of such data by well-meaning but uncritical officials and by the media would seem to make any elaboration unnecessary. None of the respondents has deigned to recognize this problem, let alone take any action to forestall such misuse of their continuing publications. Thus, if extravagant or incorrect extrapolations and causal inferences are made from the associations they have derived, they must accept their share of responsibility for this situation, which is exacting a considerable toll in unwanted pregnancies, user anxiety, and inappropriate national decisions.

We agree with Dr. Masi that "the implications (of this debate) extend beyond the matter of estimating risk or nonrisk of oral contraceptive usage per se, and relate to the total problem of clinical and population research strategy and design needed to detect uncommon and rare disease associations" and with his view that an impartial review of these questions is needed. Unfortunately, this set of letters does not begin to fill that need.

Joseph W. Goldzieher, M.D.
Tazewell S. Dozier

Division of Clinical Sciences and
Reproductive Biology
Southwest Foundation for Research and Education
P. O. Box 28147
San Antonio, Texas 78284

Oral contraceptives and thromboembolism

To the Editors:

The recent paper published in the JOURNAL, "Oral contraceptives and thromboembolism: A reassessment," by Goldzieher and Dozier,[1] is a very sad comment on the level of epidemiologic refereeing available to you. It would be hard to find an article accepted for publication in a major journal more filled with a lack of understanding of epidemiology and biostatistics, and I seriously doubt that the authors attacked should bother to point out their errors in detail. However, a statistical article of mine[2] is quoted in support of their position; therefore, I feel obliged to reply to that part of their paper.

Table I. Relationship of oral contraceptives and thromboembolism without individual matching

Diagnostic group	*Oral contraceptives*		*All women*
	Used	*Not used*	
Thromboembolism	26	32	58
Control	10	106	116
Both groups	36	138	174

Table II. Relationship of oral contraceptives and thromboembolism with individual matching

Thromboembolism patient	*Number of matched controls using oral contraceptives*			*Total*
	0	*1*	*2*	
Oral contraceptives used	21	4	1	26
Oral contraceptives not used	28	4	0	32
All thromboembolism patients	49	8	1	58

Goldzieher and Dozier maintain that, "Contrary to the opinion of Vessey, . . . there is considerable difference of opinion as to the correct statistical method to be used in analyzing data from studies where patients are matched to control subjects."[3] They are simply confused—the methods of statistical analysis expounded by Mantel and Haenszel[4] and elaborated by Miettinen[5] are almost universally accepted. It is possible that their misconception comes from a misunderstanding of what these methods accomplish, as is evident from their quoting of my paper.[2]

When case-control studies in which case subjects are individually matched to control subjects are analyzed, the proper method of analysis will take this matching into account; in 1970, I pointed this out with the use of some data on thromboembolism and oral contraceptives[6] for illustration. The data for 58 case subjects and 116 control subjects (two control subjects for each case subject) as published[6] are shown in Table I—the relative risk calculated from the table as given is $(26 \times 106)/(10 \times 32) = 8.6$. Goldzieher and Dozier rightly quote me to the effect that this is incorrect, as it ignores the individual matching, and imply indirectly that if the statistics were done correctly the increased risk of disease in oral contraceptive users would at least diminish. However, in this type of study, as I clearly indicated, the estimate of risk almost certainly increases if the calculations are done properly. Table II shows the same data as given in Table I with the matching kept intact, and the relative risk is now increased to 11.1.[5]

It is a pity that the authors talk down to their audience when they clearly do not understand these matters themselves.

Malcolm C. Pike, Ph.D.
Professor of Community Medicine and Pediatrics
University of Southern California School of Medicine
2025 Zonal Avenue
Los Angeles, California 90033

REFERENCES

1. Goldzieher, J. W., and Dozier, T. S.: Oral contraceptives and thromboembolism: A reassessment, AM. J. OBSTET. GYNECOL. **123:** 878, 1975.
2. Pike, M. C. and Morrow, R. H.: Statistical analysis of patient-control studies in epidemiology. Factor under investigation an all-or-none variable, Br. J. Prev. Soc. Med. **24:** 42, 1970.
3. Vessey, M. P.: Some methodological problems in the investigation of rare adverse reactions to oral contraceptives, Am. J. Epidemiol. **94:** 202, 1971.
4. Mantel, N., and Haenszel, W.: Statistical aspects of the analysis of data from retrospective studies of disease, J. Natl. Cancer Inst. **22:** 719, 1959.
5. Miettinen, O. S.: Individual matching with multiple controls in the case of all-or-none response, Biometrics **25:** 339, 1969.
6. Vessey, M. P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromboembolic disease, Br. Med. J. **2:** 199, 1968.

Reply to Dr. Pike

To the Editors:

It is regrettable that Dr. Pike's letter of criticism consists almost entirely of *ad hominem* invective—a fairly reliable sign that more substantial arguments are lacking. We are in no position to know whether the principles laid down by Mantel and Haenszel and other authorities are "almost universally *accepted* (italics added)," but page after page of our paper documents the fact that they are not universally *observed.* When retrospective case-control studies compare dissimilar populations, ignore wide incidence ranges in the subsets of a population, slide glibly from association to cause and effect, and extrapolate from highly selected hospital populations to the universe of contracepting women, basic principles are being grossly violated.

The point we attempted to make about matching versus nonmatching in analysis of case-control thromboembolism data was that publications, even by epidemiologists, have used the method *incorrectly.* Whether calculations yield a "relative risk" (whatever that may mean) of 8.6 or 11.1 is trivial, as neither figure conforms to reality. Others, as well as ourselves, have pointed out that the case-control approach is so flawed, both theorectically and operationally, that it should serve merely as an epidemiologic "fishing expedition," to indicate whether lengthy, expensive, but technically

less objectionable investigations are worth undertaking.

Dr. Pike's opinion of the editorial expertise of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY is not our concern. It may be of interest to others, however, that our manuscript was reviewed repeatedly during its preparation by several recognized authorities in the field of biostatistics. It was Professor Feinstein of Yale, we recall, who prophesied that we would be the "target for slings and barbs" from members of the epidemiologic fraternity outraged by criticism of one of their pet procedures. Lo, and behold!

We have a thought for Dr. Pike and others of his persuasion: Is not a discipline that strays too far from the tenets of *experimental* verification at relative risk of lapsing into pre-Baconian pseudoscience, cloaked, as usual, with impressive jargon and symbolism?

Joseph W. Goldzieher, M.D.
Tazewell S. Dozier
Division of Clinical Sciences and Reproductive Biology
Southwest Foundation for Research and Education
P. O. Box 28147
San Antonio, Texas 78284

Oral contraceptives and thromboembolism

To the Editors:

It was with great pleasure and a feeling of vindication that I read the article[1] on thromboembolism versus oral contraceptives. Long overdue recognition is given Dr. Fuertes-de la Haba and co-workers[2] who did the largest and most significant controlled study on this subject to date. They proved no relationship between a *high-dose* oral contraceptive* and thromboembolic phenomena.

The mass hysteria resulting from the publicity given to the alleged side effects of the oral contraceptives has affected even those members of our profession who are "experts" on the subject. For example, gestational diabetes[3] and overt diabetes are still being included as contraindications to the pill, despite the fact that another, equally sound study by Dr. Fuertes-de la Haba and colleagues[4] finds no relationship between the "pill" and the onset or progression of diabetes.

In addition to having a ". . . responsibility to be both widely and currently read to stay abreast of the problems in steroid contraception,"[3] the physician also has an equally important responsibility to remain objective.

Ernesto Rivera, M.D., F.A.C.O.G.
Assistant Professor
Departments of Obstetrics and Gynecology
University of Maryland School of Medicine
22 South Greene Street
Baltimore, Maryland 21202

*Enovid, 5 mg., G. D. Searle & Co., P. O. Box 5110, Chicago, Illinois 60680.

REFERENCES

1. Goldzieher, J. W., and Dozier, T. S.: Oral contraceptives and thromboembolism: A reassessment, AM. J. OBSTET. GYNECOL. **123:** 878, 1975.
2. Fuertes-de la Haba, A., Curet, J. O., Pelegrina, I. et al.: Thrombophlebitis among oral and non-oral contraceptive users, Obstet. Gynecol. **37:** 259, 1971.
3. Panel discussion: Clinical perspective on the pill, Dialogues in Oral Contraception, **1:** 1, 1975.
4. Fuertes-de la Haba, A., Vega-de Rodringuez, G., and Pelegrina, I.: Carbohydrate metabolism in long-term oral contraceptive users, Obstet. Gynecol. **37:** 220, 1971.

Infusion of bicarbonate into newborn infants

To the Editors:

I would like to comment on the article "Rapid infusion of sodium bicarbonate and albumin into high-risk premature infants soon after birth: A controlled, prospective trial," by Drs. Bland, Clarke, and Harden (AM. J. OBSTET. GYNECOL. 124: 263, 1976). I believe that the authors have missed the point of infusion of bicarbonate into newborn infants and may discourage the use of very valuable technique. I am in full agreement that routine infusion of bicarbonate into premature babies will not decrease the incidence of respiratory distress syndrome; however, the delivery room use of bicarbonate for the proper indications may be life-saving.

I am distressed to see the authors infusing bicarbonate-containing solutions into newborn infants who are not acidotic. The studies of Finberg that were cited in the article did indeed show that nonacidotic kittens are more likely to have intracranial hemorrhages when they receive bicarbonate (although that study involved the use of massive doses of bicarbonate.[1] The proposed mechanism of cerebral hemorrhage is sudden dehydration of the brain from increased osmolality. Since acidotic newborn infants are likely to have cerebral edema, this is not likely to be a problem. Further, acidotic neonates have pulmonary vasoconstriction and need pH correction in order to reverse fetal shunts. Our work with fetal lambs has shown that doses of bicarbonate far above those used in the clinical situation do not increase the incidence of cerebral hemorrhage and do make resuscitation more successful.[2, 3] The whole key is that bicarbonate should be given for an indication, that is, acidosis.

The incidence of cerebral hemorrhage in the authors' series was not really statistically significantly greater in the bicarbonate group according to their own data. Further, since intracranial hemorrhage may be associated with hypoxia, regardless of treatment, the authors' lack of P_{O_2} data makes interpretation very difficult.

I am also in agreement with the authors' observation that P_{CO_2} will increase after bicarbonate infusion *without ventilation*. However, depressed newborn infants should be ventilated, and as long as ventilation is adequate P_{CO_2} will not increase. Incidentally, the in-

crease in P_{CO_2} that the authors noticed in their series would not be enough to increase cerebral blood flow to the point of causing intracranial hemorrhage.[4]

Additionally, since increased serum sodium and osmalality have been incriminated as a cause of intracranial hemorrhage in the neonate, the authors' lack of determination of these parameters also detracts from their conclusions.

Again, I am not advocating indiscriminate use of bicarbonate infusion in high-risk premature newborn infants, particularly since premature infants do have an increased incidence of cerebral hemorrhage. However, I am strongly advocating infusion of bicarbonate in newborn infants who are acidotic. The ideal way to determine whether or not infusion is needed is by determination of arterial blood gases by means of scalp sampling prior to delivery or sampling of cord blood after delivery. If this is not possible, the data are such that one can assume neonates with Apgar scores of 2 or less at one minute or 5 or less at five minutes are acidotic and will benefit by bicarbonate infusion.[5]

Finally, I certainly agree that further controlled prospective trials are needed, however, with the indications for bicarbonate infusion perhaps spelled out a little more clearly.

Jay S. DeVore, M.D.
Eveline A. Ricciarelli, M.D.

Department of Anesthesiology
Prentice Women's Hospital and Maternity Center
Northwestern Memorial Hospital
333 East Superior Street
Chicago, Illinois 60611

REFERENCES

1. Luttrell, C. N., Finberg, L., and Drawdy, L. P.: Hemorrhagic encephalopathy induced by hypernatremia. II. Experimental observations on hyperosmolality in cats, Arch. Neurol. **1:** 153, 1959.
2. Ricciarelli, E., Gutsche, B., DeVore, J. S., and Shapiro, H.: The effect of epidural analgesia on fetal and neonatal status, *in* Abstracts of Scientific Papers, 1974 Annual Meeting, American Society of Anesthesiologists, p. 295.
3. Wheeler, A. S., DeVore, J. S., Sadri, S., David-Mian, Z., Latyshevsky, H., Miller, A., and Gutsche, B. B.: The effects of intravenous sodium bicarbonate in the neonatal lamb partially asphyxiated in utero, *in* Abstracts of Scientific Papers, 1975 Annual Meeting, American Society of Anesthesiologists.
4. Kety, S. S., and Schmidt, C. F.: The effects of altered arterial tensions of carbon dioxide on cerebral blood flow and cerebral oxygen consumption of normal young men, J. Clin. Invest. **27:** 484, 1948.
5. Tooley, W. H.: Alkali therapy in the asphyxiated newborn infant, *in* Schnider, S. M., editor: Obstetrical Anesthesia, Current Concepts and Practice, Baltimore, 1970, The Williams & Wilkins Company.

Reply to Drs. DeVore and Ricciarelli

To the Editors:

We recognize that our prospective trial of alkali infusions into high-risk, premature infants was not flawless, as we carefully pointed out in the "Comment" section of our paper. The results might have been more convincing if we had measured serum sodium concentrations, arterial blood pressures, and oxygen tensions before and after each infusion, if we had included only those babies with pH measurements below 7.20, and if we had studied 100 infants instead of only 53. To our knowledge, however, this trial of alkali infusions was the first of its kind to include a suitable control group and a substantial number of patients; therefore, it seemed worthy of a brief communication. Skeptics and seasoned "bicarb pushers" will be reluctant to accept the results of any study which questions the efficacy of a major ingredient in the cookbook armamentarium against neonatal asphyxia and respiratory distress. But, to be fair, Drs. DeVore and Ricciarelli should re-examine the facts of our report.

Twenty-six infants received alkali-containing and 27 received non–alkali-containing solutions within the first two hours of life—the infants were born prematurely and had low serum protein concentrations, and they were treated by random selection. The average pH of infants who received sodium bicarbonate was 7.25 ± 0.03, a figure which most people regard as showing acidemia; only five had pH values above 7.30, and all of these infants had a good outcome. In other words, 21 of 26 infants who received alkali had initial pH measurements below 7.30; 11 of these infants died, and four had intracranial hemorrhage. In contrast to these results, 18 "control" infants had pH measurements below 7.30 (average for all 27 "control" babies was 7.26 ± 0.03), and, of these, five died and none had intracranial hemorrhage. While the differences are not statistically significant at the 0.05 level, as we stated in the paper, the results do not support the usefulness of alkali in treating preterm infants with acidemia; furthermore, they support, *with controls,* the suggestion of others[1–4] that such infusions may be harmful.

The comment by Drs. DeVore and Ricciarelli that ". . . acidotic newborn infants are likely to have cerebral edema. . ." and cerebral hemorrhage ". . . is not likely to be a problem" is conjectural and inconsistent with the *fact* that such bleeding *is* a problem. Certainly, pulmonary vasoconstriction must be corrected, but the studies of Malik and Kidd[5] demonstrated that hypoxic pulmonary vasoconstriction is CO_2-dependent and not pH-dependent; therefore, ventilation should be the therapeutic approach, perhaps with suitable plasma volume expansion if hypotension ensues, rather than the additional CO_2 delivered by an infusion of sodium bicarbonate.

The finding that newborn lambs do not suffer from intracranial hemorrhage despite administration of sodium bicarbonate is not reassuring; it only emphasizes the resilience of the newborn lamb—differences in cerebral anatomy and maturity make such a comparison misleading. Again, the fact is that

preterm infants with acidemia are subject to intracranial hemorrhage, but we saw this *only* after infusions of hypertonic alkali.

Drs. DeVore and Ricciarelli suggest that cerebral blood flow in preterm infants is not increased with $Paco_2$ measurements between 50 and 60 torr. Kety and Schmidt dealt with normal young men, not prematurely born infants. Is the comparison valid and should we assume that these CO_2 measurements were the peak levels for these infants?

We hope that Drs. DeVore and Ricciarelli will design a better study than ours to resolve this important issue. Until that time, we recommend restraint in the use of alkali to manage acidemia in preterm infants, particularly those in whom ventilation may be impaired.

Richard D. Bland, M.D.
Assistant Professor of Pediatrics
Cardiovascular Research Institute
University of California, San Francisco
San Francisco, California 94143

REFERENCES

1. Simmons, M. A., Adcock, E. W., Bard, H., and Battaglia, F. C.: Hypernatremia and intracranial hemorrhage in neonates, N. Engl. J. Med. **291:** 6, 1974.
2. Usher, R.: Treatment of respiratory distress syndrome, *in* Winters, R. W., editor: The Body Fluids in Pediatrics, Boston, 1973, Little, Brown, & Company, pp. 303-337.
3. Finberg, L.: Dangers to infants caused by changes in osmolal concentration, Pediatrics **40:** 1031, 1967.
4. Ostrea, E. M., and Odell, G. B.: The influence of bicarbonate administration on blood pH in a "closed system": Clinical implications, J. Pediatr. **80:** 671, 1972.
5. Malik, A. B., and Kidd, B. S. L.: Independent effects of changes in H^+ and CO_2 concentrations on hypoxic pulmonary vasoconstriction, J. Appl. Physiol. **34:** 318, 1973.

Ninth Annual North Memorial Medical Center Symposium on Obstetrics and Gynecology

The Ninth Annual North Memorial Medical Center Symposium on Obstetrics and Gynecology will be held December 3, 1976, in Minneapolis, Minnesota. Faculty for the Symposium include: Norman F. Gant, M.D., from the University of Texas; Roy M. Pitkin, M.D., from the University of Iowa; Jack R. Robertson, M.D., from Santa Maria, California; Douglas R. Shanklin, M.D., from the University of Chicago; and Barry S. Schifrin, M.D., from Los Angeles, California. For further information, contact: Dr. Harry Farb, Symposium Program Director, 103 Oakdale Medical Center, Minneapolis, Minnesota 55422.

ITEMS

Eastern Student Research Forum

The Eastern Student Research Forum will be presented at the University of Miami School of Medicine, February 20-22, 1977. Deadline for submission of abstracts is November 15, 1976. There will be Excellence in Research Awards and other categorical awards as well as cash awards. The Forum is open to all medical and graduate students. For further information, contact: ESRF, P. O. Box 520875, Biscayne Annex, Miami, Florida 33152. Telephone: (305) 547-6811.

Child Health in America

"Child Health in America," a bicentennial brochure of the United States Department of Health, Education, and Welfare, tells the story of the Nation's efforts to minister to the health needs of its infants and children. Single copies of "Child Health in America" are available without charge from the Program Services Branch, Bureau of Community Health Services, Health Services Administration, Room 7A20, 5600 Fishers Lane, Rockville, Maryland 20852.

Pediatric Critical Care

A program entitled "Pediatric Critical Care" will be presented November 19 and 20, 1976, at The Cosmopolitan Hotel, Denver, Colorado, in the Century Room. On Friday, November 19, the program will be presented from 8 A.M. to 4 P.M., and on Saturday, November 20, it will be presented from 8 A.M. to 12 noon. For further information and registration, contact: MaryAnn Van Gorp, Department of Continuing Education, The Children's Hospital, 1056 E. Nineteenth Ave., Denver, Colorado 80218. Telephone: (303) 861-8888, Ext. 2280.

Legislative Issues in Maternal/Child Health

A program entitled "Legislative Issues in Maternal/Child Health" will be presented December 10, 1976, in the Tammen Auditorium, The Children's Hospital, Denver, Colorado, from 8 A.M. to 4 P.M. For further information and registration, contact: MaryAnn Van Gorp, Department of Continuing Education, The Children's Hospital, 1056 E. Nineteenth Ave., Denver, Colorado 80218. Telephone: (303) 861-8888, Ext. 2280.

The Fourteenth Congress of The Pan-Pacific Surgical Association

The Fourteenth Congress of The Pan-Pacific Surgical Association will be held April 1-7, 1978, at the Hilton Hawaiian Village Hotel, Honolulu, Hawaii. Concurrent meetings will be held in: General Surgery, Neurosurgery, Obstetrics and Gynecology, Ophthalmology, Orthopedic Surgery, Otolaryngology, Plastic Surgery, Thoracic-Cardiovascular, and Urology. For further details, write: Cesar B. deJesus, M.D., Pan-Pacific Surgical Association, 236 Alexander Young Bldg., Honolulu, Hawaii 96813.

Annual Meeting of the Society for Obstetric Anesthesia and Perinatology

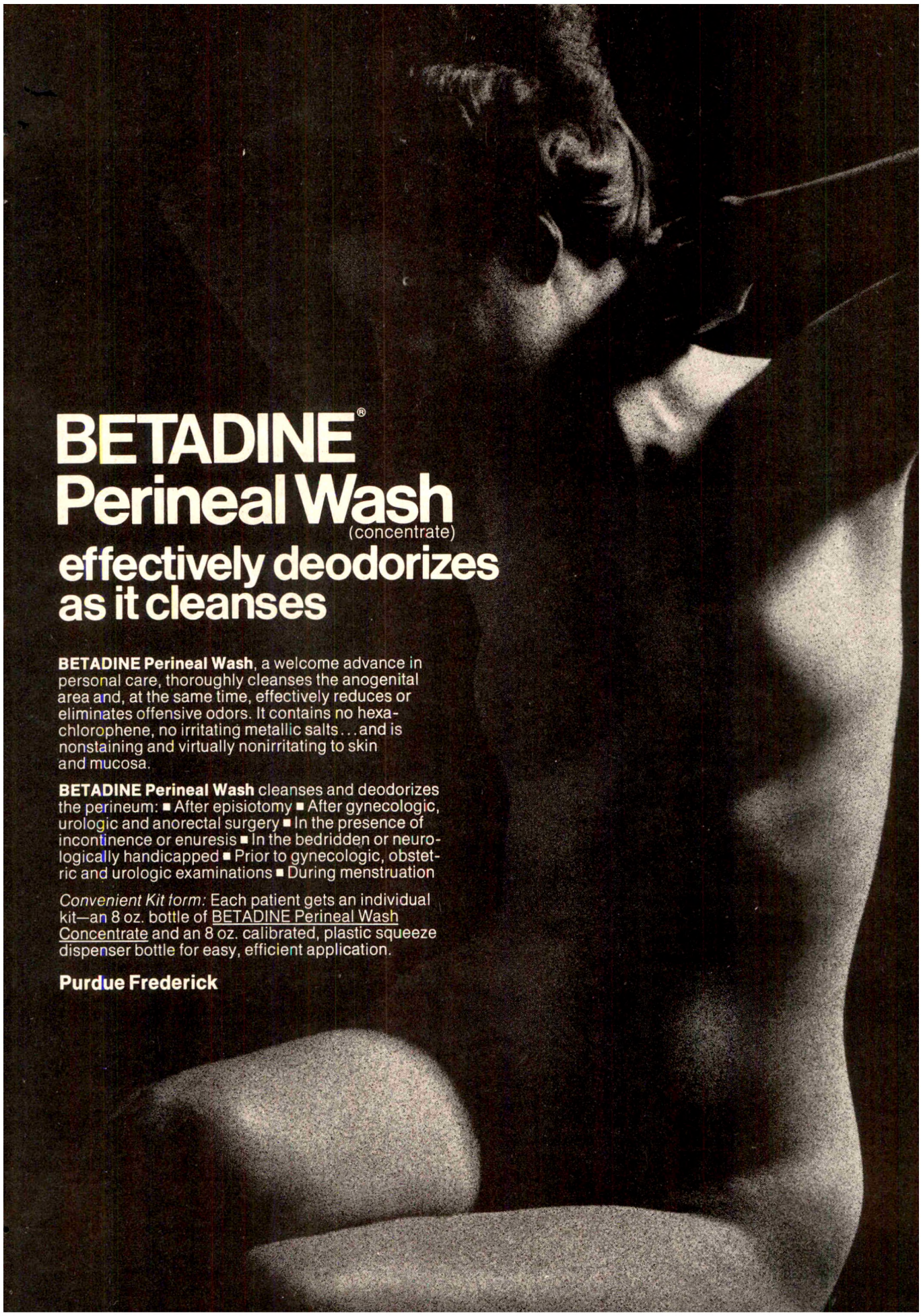
The Annual Meeting of the Society for Obstetric Anesthesia and Perinatology will be held April 14-17, 1977, at the Edgewater Inn, Seattle, Washington. For more information, write: David Ralston, M.D., Department of Anesthesia, University of Washington, School of Medicine, Seattle, Washington 98105.

VIIIth Meeting of the International Study Group for Steroid Hormones

The VIIIth Meeting of the International Study Group for Steroid Hormones will be held in Rome in December, 1977. It will be dedicated to: (1) control mechanisms of reproductive function, and (2) recent trends in steroid methodology. For further information and a preliminary program, please contact: Prof. Carlo Conti, International Study Group for Steroid Hormones, Istituto di Patologia Medica II, Policlinico Umberto 1, Università di Roma, Rome, Italy.

Sixth Asia and Oceania Congress of Endocrinology

Singapore has been selected as the site of the Sixth Asia and Oceania Congress of Endocrinology, organized by the Endocrine and Metabolic Society of Singapore. The Congress will be held January 22 to 27, 1978, and the Asia and Oceania Thyroid Association will meet concurrently. For further information, please write to: Dr. J. A. Tambyah, The Secretariat, Sixth Asia and Oceania Congress of Endocrinology, c/o Academy of Medicine, 4-A College Rd., Singapore 3, Republic of Singapore.



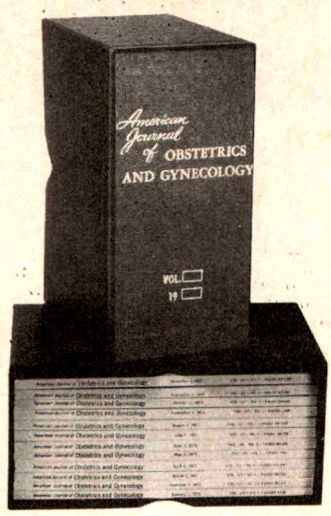
BETADINE® Perineal Wash (concentrate) effectively deodorizes as it cleanses

BETADINE Perineal Wash, a welcome advance in personal care, thoroughly cleanses the anogenital area and, at the same time, effectively reduces or eliminates offensive odors. It contains no hexachlorophene, no irritating metallic salts…and is nonstaining and virtually nonirritating to skin and mucosa.

BETADINE Perineal Wash cleanses and deodorizes the perineum: ■ After episiotomy ■ After gynecologic, urologic and anorectal surgery ■ In the presence of incontinence or enuresis ■ In the bedridden or neurologically handicapped ■ Prior to gynecologic, obstetric and urologic examinations ■ During menstruation

Convenient Kit form: Each patient gets an individual kit—an 8 oz. bottle of BETADINE Perineal Wash Concentrate and an 8 oz. calibrated, plastic squeeze dispenser bottle for easy, efficient application.

Purdue Frederick



PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Two files hold an entire year's issues. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only $4.25 each, postpaid (3 for $12., 6 for $22.). Add $1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141

Please send me, postpaid _____ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at $4.25 each (3/$12., 6/$22.)

☐ NEW SIZE (8¼" × 11") for 1975 copies
☐ OLD SIZE (7¼" × 10½") for copies prior to 1975

Name _____

Address _____

City _____ State _____ Zip _____

Flagyl®

(metronidazole) 250 mg.

Warning

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

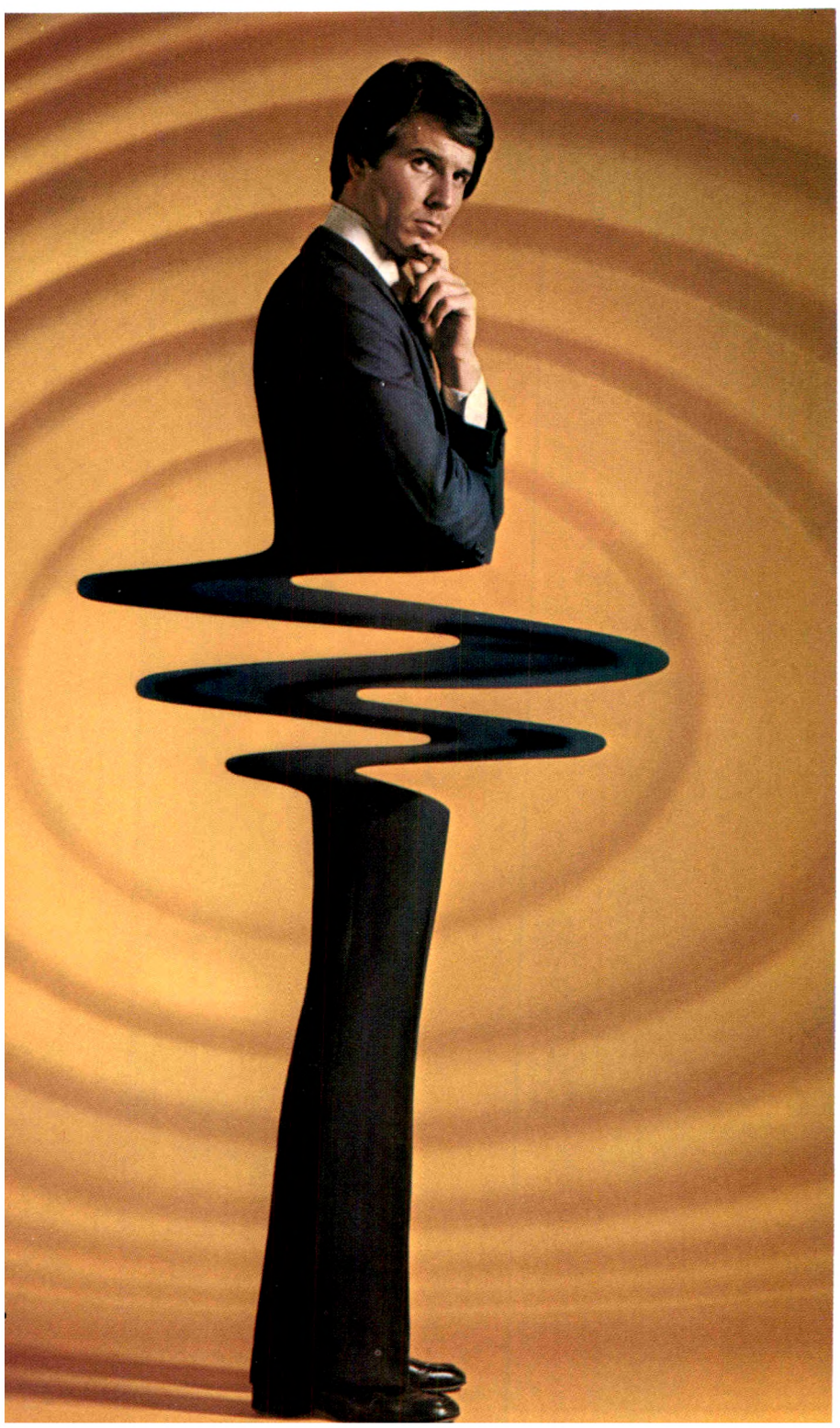
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co.

If men suffered from the symptoms of trichomoniasis, they'd appreciate Flagyl®.

(metronidazole)



Women with trichomoniasis have been grateful for the benefits of Flagyl therapy for over a decade. Most men have no symptoms and are not even aware that they have contracted trichomoniasis, so they rarely appreciate Flagyl. Unless both sexual partners are diagnosed and treated simultaneously, reinfection from the consort is a probability (the "ping-pong" effect).

In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra and the bladder. Only the systemic action of Flagyl can eliminate trichomonads from these sequestered sites.

In the male, only Flagyl can effectively eliminate trichomonac from the male genitourinary trac

Thus, for the female Flagyl is the treatment of choice. For the male it is the only choice. And that's something they both can appreciate!

Flagyl®
(metronidazole)
250-mg. tablets

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Please see adjacent page for brief summary of prescribing information.

Happy homecoming for the new mother



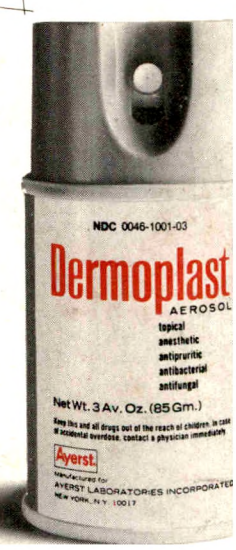
For continued relief of postepisiotomy discomfort, send her home from the hospital with DERMOPLAST® Aerosol

What DERMOPLAST starts doing to relieve postepisiotomy discomfort in the hospital, it can keep doing at home—to help make the new mother's first days with her baby as enjoyable as they should be. DERMOPLAST permeates the suture line without affecting sutures, and relieves itching that accom-

It will not dry or macerate the skin, and is easily removed with soap and water. DERMOPLAST is easy to apply—sprays from any angle. Available in three sizes, including convenient 3-oz. size that is especially designed for self-administration by the patient.

DERMOPLAST Aerosol Spray contains: Benzocaine, w/w 4.5%; benzethonium chloride, w/w 0.1%; menthol, w/w 0.5%; oxyquinoline benzoate, w/w 1.2%; and methylparaben, w/w 2.0%. Inactive ingredients, vegetable oils and propellant. Also contains 1.9% isopropyl alcohol.

For additional indications, full directions for use, and warnings, see label copy on DERMOPLAST Aerosol Spray can.



Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

7535

22.3.77

November 15, 1976
volume 126, number 6

American Journal of OBSTETRICS AND GYNECOLOGY

Copyright © 1976 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors
FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Editors Emeritus
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

Official Publication

AMERICAN GYNECOLOGICAL SOCIETY
AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY



Published by
THE C. V. MOSBY COMPANY
St. Louis, Missouri 63141

AJOGAH 126 (6) 627-738 (1976)

LIBRARY



Now, the flexibilit you need.

New, improved insertion instrument simplifies accurate fundal placement.

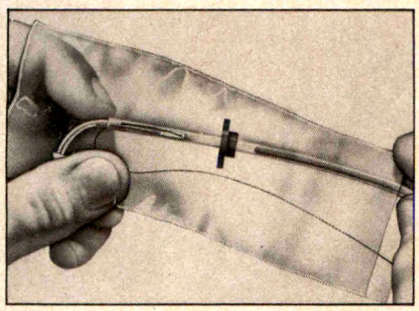
Our Cu-7 insertion instrument has been completely redesigned and engineered to facilitate accurate fundal placement. Using the recommended procedure, Cu-7 positioning can now be accomplished in just seconds, usually with minimal patient discomfort.

The Cu-7 itself offers reliable, comfortable protection from pregnancy, rivaling "the pill" as a method of choice for nulliparous as well as multiparous women.

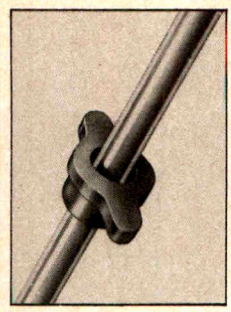
Your Searle representative is eager to advise you of the correct steps required for simple insertion of the Cu-7. Please ask for a demonstration—and for Patient Logs and booklets.

Cu-7®
intrauterine copper contraceptive

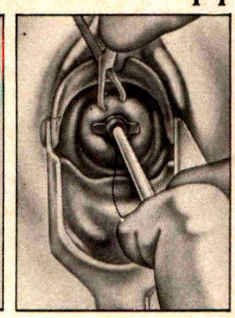
How five newly designed features make it easier to use Cu-7® intrauterine copper contraceptive.



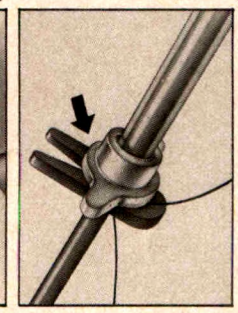
1. New sterile sheath
Helps maintain sterility during loading procedure and cervical-stop setting.



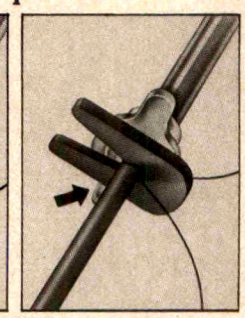
2. New blue-winged cervical stop
A visual guide to aid in correct positioning of the "seven" in the uterus.



3. New flexible rod
Facilitates insertion of "seven" into virtually any normal uterine cavity in seconds.



4. New welded tube-stop
Serves as handle for withdrawing the tube and removal of instrument.



5. New thread-retaining clip
When held to tube-stop during procedure, facilitates insertion and makes tube-crimping virtually impossible.

Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is 89 mg. of pure, virgin electrolytic copper wire providing 200mm^2 of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the copper coil into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication: The Cu-7 is indicated for contraception.

Contraindications: The presence of any of the following, at the time of insertion, constitutes a contraindication: pregnancy, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months, endometrial disease such as hyperplasia or carcinoma and a known or suspected allergy to copper.

Warnings: Recent reports suggest an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. In some cases, initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned of the suggested incidence of increased risk of sepsis and followed with close vigilance.

The long-term effects on the offspring of the presence of copper in the uterus during pregnancy are unknown.

Perforations of the uterus have occurred. In this case the device should be removed immediately.

The use of microwave therapy in patients with metal prosthetics may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients wearing a Cu-7.

Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease, the incidence of which is one in two hundred thousand.

Precautions: A pelvic examination should be done.

Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed shortly following a menstrual period. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed.

Occasional perforations of the uterus (.03%) have been reported, usually during insertion into patients less than two months post abortion or post partum. If penetration into abdominal cavity occurs, laparotomy should be performed and the device recovered. Local inflammatory reaction with abscess formation is a possibility if a device is left in the abdomen.

If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

The Cu-7 should be removed if pelvic infection which is unresponsive to treatment occurs.

The device should be replaced every two years. There is no evidence of decreasing effectiveness with time before two years, but the contraceptive effectiveness of the Cu-7 after two years has yet to be established.

If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to pull on the thread and displace the Cu-7 and told to return in two years for its replacement.

A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman wearing a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being worn.

Adverse Reactions: Perforation of the uterus has occurred.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women.

Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Transient spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. The following complaints have also been reported, although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, and cystitis.

Dosage and Administration: A single Cu-7 is to be inserted into the uterine cavity (see Precautions section). The small diameter of the Cu-7 enables easy insertion into the nulliparous as well as the multiparous uterus. Present information indicates that the efficacy is retained for at least 24 months. Until accurate data indicating a longer effective life become available, the Cu-7 should be removed and a new one inserted on or before 24 months from the date of insertion. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

How Supplied: Available in cartons of 6 and boxes of 30 sterile units (Cu-7 with an inserter) and sufficient patient identification cards.

Clinical Studies: Different event rates have been recorded with the use of different intrauterine contraceptive devices, inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use.) This experience encompasses 321,699 woman-months of use, including 12 months for 9,594 women and 24 months for 7,599.

	12 Months		24 Months	
	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.7	1.3	2.5	2.1
Expulsion	5.5	7.7	6.5	8.7
Medical Removal	9.6	12.7	15.3	18.2
Continuation Rate	78.3	72.9	63.9	59.7

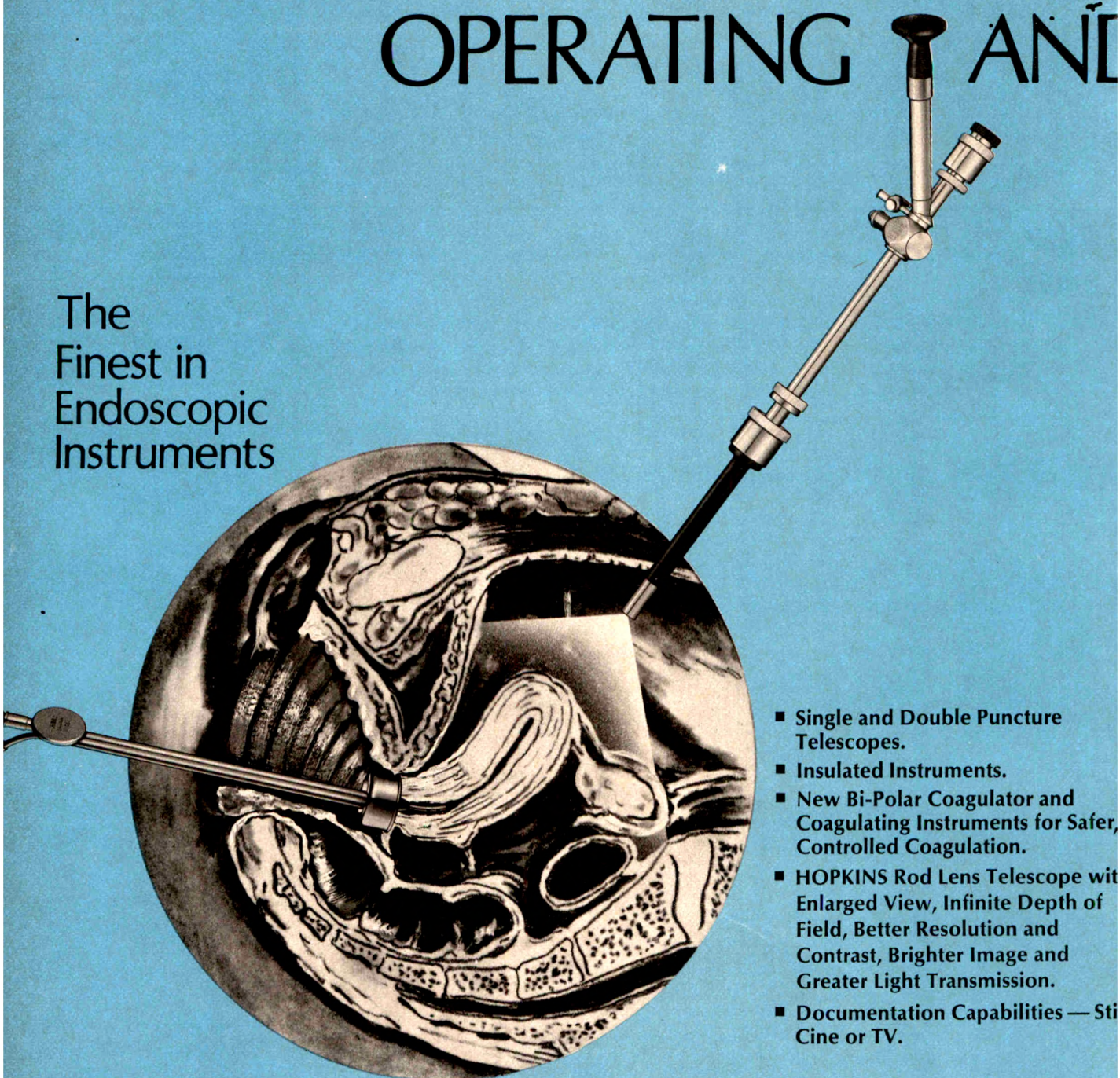
Please see complete product labeling for insertion and removal techniques.

SEARLE **Searle Laboratories**
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

6B1-R1

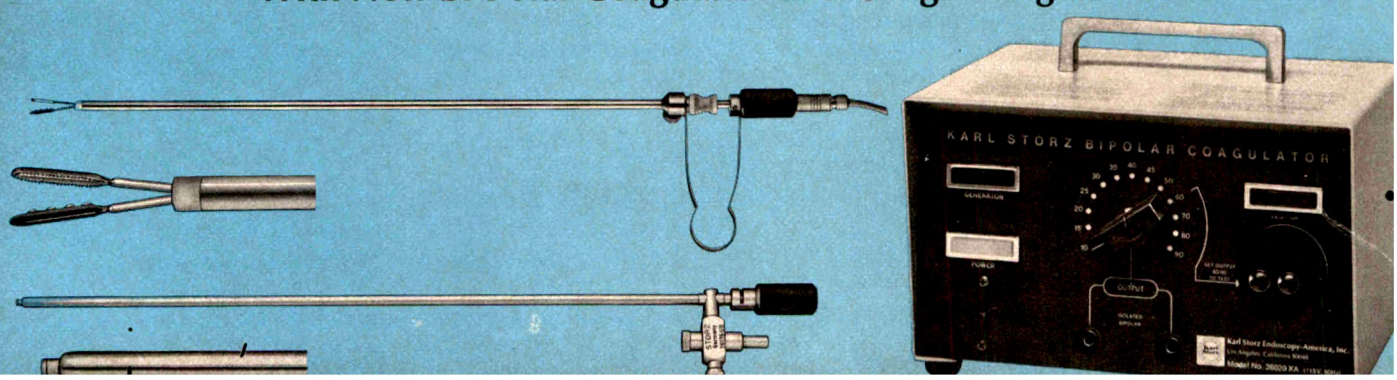
NEW LAPAROSCOPES! OPERATING AND

The Finest in Endoscopic Instruments

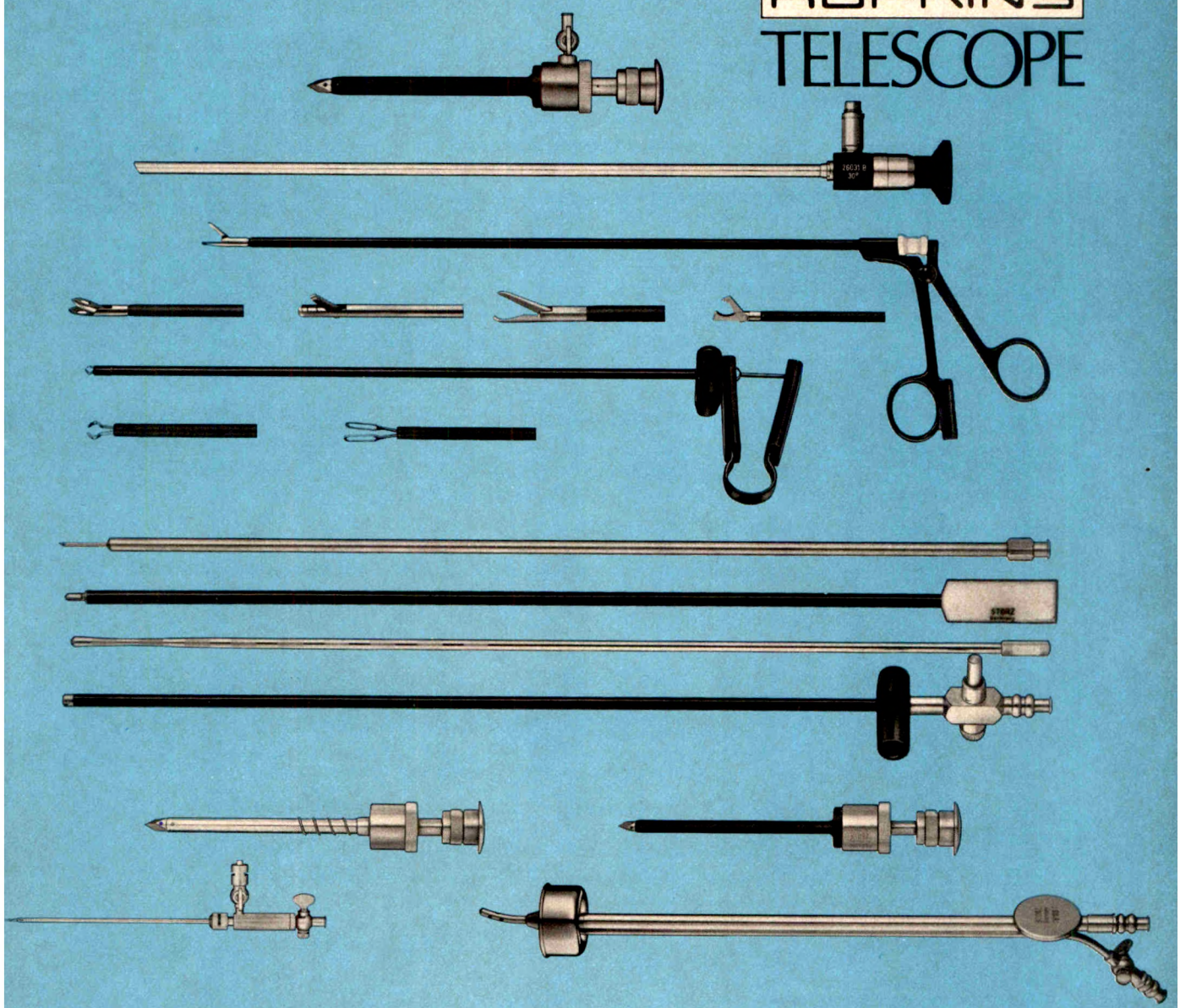


- Single and Double Puncture Telescopes.
- Insulated Instruments.
- New Bi-Polar Coagulator and Coagulating Instruments for Safer, Controlled Coagulation.
- HOPKINS Rod Lens Telescope wit Enlarged View, Infinite Depth of Field, Better Resolution and Contrast, Brighter Image and Greater Light Transmission.
- Documentation Capabilities — Sti Cine or TV.

With New Bi-Polar Coagulator and Coagulating Instruments



ENLARGED VIEW from Karl Storz with HOPKINS TELESCOPE



Karl Storz Endoscopy—America, Inc.
658 South San Vicente Blvd., Los Angeles, Ca. 90048

FOR TOLL FREE SERVICE 800-421-0837
(Except California) In Calif. CALL (213) 651-1068

Gentlemen:

☐ Please send me latest brochure and prices. ☐ Please have a Karl Storz Representative phone me for an appointment.

Thank you

Name (please print)

Address

City State Zip

The causes of vaginitis are multiple



You can depend on AVC... therapy that combats major vaginal pathogens and provides rapid symptomatic relief.*

***Indications:** Based on a review of AVC by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: For the relief of symptoms of vulvovaginitis where isolation of the specific organism responsible (usually *Trichomonas vaginalis*, *Candida albicans*, or *Hemophilus vaginalis*) is not possible.

NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Known sensitivity to sulfonamides.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.

Dosage: 1 applicatorful (about 6 g.) or 1 suppository intravaginally once or twice daily.

Supplied: Cream–4 ounce tube with applicator. Suppositories–Box of 16 with inserter.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

4-6744 (6049)

The treatment is singular

AVC™

Cream (aminacrine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%)

Suppositories (aminacrine hydrochloride 0.014 g., sulfanilamide 1.05 g., allantoin 0.14 g.)

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Contents

November 15

1976

Clinical opinion

Obstetrician-gynecologists are primary physicians to women. I. Practice patterns of Michigan obstetrician-gynecologists 627

J. Robert Willson, M.D., and David M. Burkons, M.D.

Ann Arbor, Michigan

The laparoscopist and electrosurgery 633

John M. Esposito, M.D.

Brooklyn, New York

Gynecology

Plasma levels of fractionated estrogens and pituitary hormones in endometrial carcinoma 638

Fred Benjamin, M.D., and Stanley Deutsch, Ph.D.

Jamaica, New York

(Contents continued on page 7)

Vol. 126, No. 6, November 15, 1976. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

Annual subscription rates.

	U. S.	*PUAS,* Mexico*	*Canada, other countries*
Institutional**	$40.50	$52.50	$54.50
Personal†	$28.50	$40.50	$42.50
Student, intern, resident†	$22.80	$34.80	$36.80

*(*Postal Union of the Americas and Spain)*

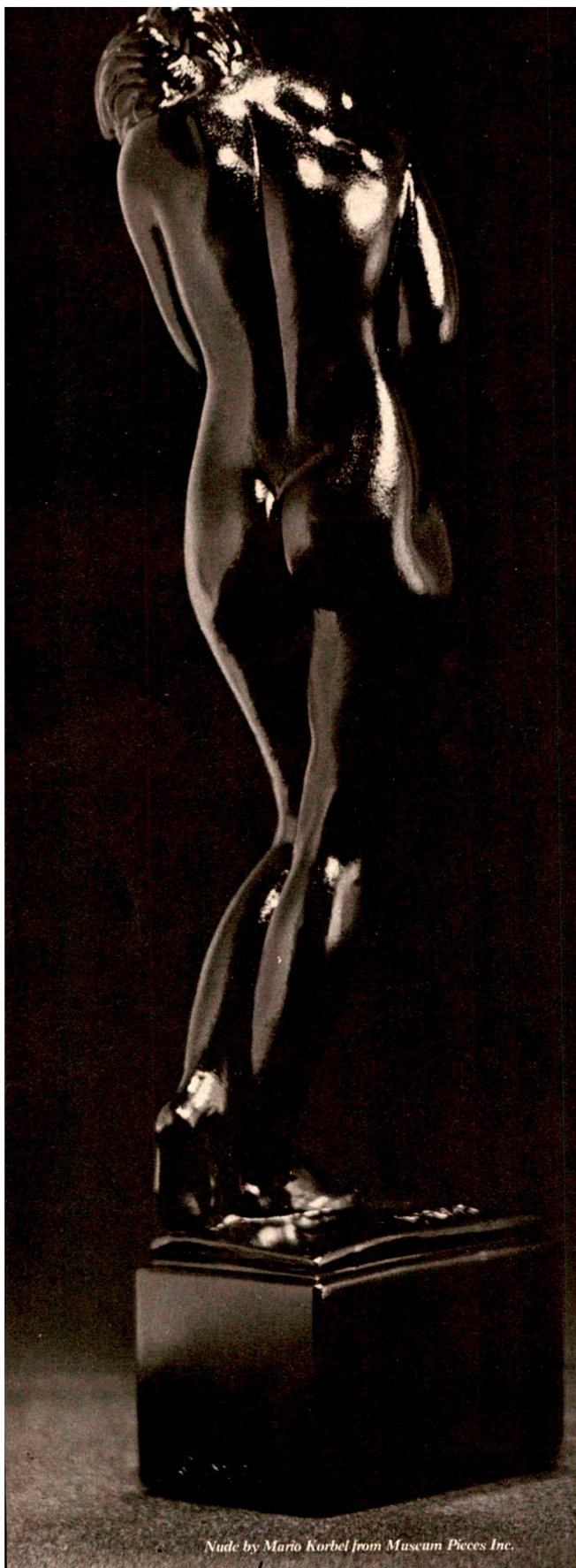
Single copies are $4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

**Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Missouri. Printed in the U. S. A. Copyright © 1976 by The C. V. Mosby Company.



Nude by Mario Korbel from Museum Pieces Inc.

True human estrogen replacement

Hormonin
(estriol, estradiol, estrone)

BRIEF SUMMARY: See package insert for full prescribing information.

CHOOSE FROM TWO CONVENIENT ORAL FORMS:

HORMONIN NO. 1 (half strength)	*HORMONIN NO. 2 (full strength)*
Each Tablet Contains:	*Each Tablet Contains:*
ESTRIOL 0.135 mg.	*ESTRIOL 0.27 mg.*
ESTRADIOL 0.3 mg.	*ESTRADIOL 0.6 mg.*
ESTRONE 0.7 mg.	*ESTRONE 1.4 mg.*

INDICATIONS: Replacement therapy for naturally occurring or surgically induced estrogen deficient states, including the menopause syndrome and post-menopausal conditions.

CONTRAINDICATIONS: Women having familial or personal history of mammary or genital cancer.

PRECAUTIONS: Estrogen should not be administered to women with recurrent mastitis or abnormal mammograms except in instances where the physician feels that treatment is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen dependent neoplasia.

The physician should be alert to the earliest manifestation of thrombotic disorders. Should this problem occur, discontinue estrogen therapy immediately. The long range effect of estrogen on nursing infants has not been established.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer of hypercalcemia, estrogen administration should be discontinued. The use of any estrogen in pregnancy is not recommended.

A complete pretreatment physical examination should be performed with special reference to the pelvis and breast. To avoid continuous stimulation of the uterus and breast, cyclic therapy is recommended (3 weeks on medication and 1 week off). Withdrawal bleeding may occur during the one week off medication. If unexplained or excessive vaginal bleeding occurs, the physician should check for the organic pathology.

Pre-existing fibromyomata may increase in size while using estrogen. For this reason, patients should be examined at regular intervals. Treatment with estrogen may mask the onset of the climacteric. Certain liver and endocrine function tests may be affected by exogenous estrogen administration.

DOSAGE: Orally, for the relief of menopausal symptoms, HORMONIN NO. 1, 1 or 2 tablets daily according to severity of symptoms; HORMONIN NO. 2, 1 tablet daily. The initial dosage may be decreased to establish maintenance dosage. To avoid possible continuous stimulation of the breast and uterus, cyclic therapy may be employed. In severe cases, initial therapy may be supplemented with parenteral estrogens.

CARNRICK LABORATORIES

DIV. G. W. CARNRICK CO., 65 HORSE HILL ROAD, CEDAR KNOLLS, N.J. 07927

Contents continued from page 5

Untreated endocervical gonorrhea and endometritis following elective abortion 648
Ronald T. Burkman, M.D., James A. Tonascia, Ph.D.,
Milagros F. Atienza, M.D., and Theodore M. King, M.D., Ph.D.
Baltimore, Maryland

Amylases of the genital tract. I. Isoamylases of genital tract tissue homogenates and peritoneal fluid 652
G. Skude, M.D., P.-A. Mårdh, M.D., and L. Weström, M.D.
Malmö and Lund, Sweden

Amylases of the genital tract. II. Peritoneal fluid isoamylases in acute salpingitis 657
L. Weström, M.D., G. Skude, M.D., and P.-A. Mårdh, M.D.
Lund and Malmö, Sweden

Immunologic studies in patients with trophoblastic neoplasia 661
Yutaka Tomoda, M.D., Masakazu Fuma, M.D., Norihiko Saiki, M.D.,
Naotaka Ishizuka, M.D., and Tatsuya Akaza
Nagoya, Japan

Fertility in women with gonadal dysgenesis 668
F. I. Reyes, M.D., K. S. Koh, M.D., B.S., and C. Faiman, M.D., M.Sc.
Winnipeg, Manitoba, Canada

Obstetrics

Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes 671
Kent Ueland, M.D.
Seattle, Washington

Serum human chorionic gonadotropin levels throughout normal pregnancy 678
Glenn D. Braunstein, M.D., Joan Rasor, M.A., Donald Adler, M.D.,
Hal Danzer, M.D., and Maclyn E. Wade, M.D.
Los Angeles, California

Uterine activity in the multiparous patient 682
James R. Huey, Jr., Lieutenant Colonel, USAF, MC,
Alexander Al-Hadjiev, M.D., and Richard H. Paul, M.D.
Los Angeles, California

Maternal deaths in Texas, 1969 to 1973 687
C. E. Gibbs, M.D., and William E. Locke, M.D.
San Antonio, Texas

(Contents continued on page 9)

In routine and resistant vaginal moniliasis...

MONISTAT CREAM
TRADEMARK

(MICONAZOLE NITRATE 2%)



significantly high cures after one course of therapy

high cure rates in the pregnant,† the non-pregnant, women on antibiotic therapy, women previously treated with other antifungal agents

negative cultures usually maintained 30 days or more post-therapy

usually works in one course of therapy with a simple once-daily h.s. dosage for 14 days

soothing, non-staining cream also may be used on external vulva

†Monistat Cream may be used in the second and third trimesters. However, in the first trimester, it should be used only when the physician considers it essential to the patient's welfare.

Description MONISTAT (miconazole nitrate 2%) is a water-miscible, white cream containing as the active ingredient, 2% miconazole nitrate, 1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy) phenethyl] imidazole nitrate.

Actions MONISTAT Cream exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown.

Indications MONISTAT Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis).

As MONISTAT Cream is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis*) should be ruled out by appropriate laboratory methods.

MONISTAT is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See PRECAUTIONS.)

Contraindication Patients known to be hypersensitive to this drug.

Precautions *General:* Discontinue drug if sensitization or irritation is reported during use. *Laboratory Tests:* If there is a lack of response to MONISTAT, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens. *Pregnancy:* MONISTAT Cream was used in 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women. Since MONISTAT Cream is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient.

Adverse Reactions Thirty-nine (7.4%) of the 528 patients treated with MONISTAT reported complaints during therapy that were possibly drug-related. Most complaints were reported during the first week of therapy. Vulvovaginal burning, itching or irritation occurred in 6.6%, while other complaints such as vaginal burning, pelvic cramps, hives, skin rash and headache occurred rarely (each less than 0.2% patient incidence). The therapy-related dropout rate was 0.9%.

Dosage and Administration One applicatorful is administered intravaginally once daily at bedtime for 14 days. Course of therapy may be repeated after other pathogens have been ruled out by appropriate smears and cultures.

Supplied MONISTAT Cream is available in 3 oz. (85 g) tubes with Ortho* Measured Dose Applicator.

MONISTAT (Miconazole Nitrate 2%) is a development of Ortho Pharmaceutical Corporation and Janssen Pharmaceutica, Belgium.

*TRADEMARK

© OPC 1976

OJ260-5R2

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Contents continued from page 7

A new, more sensitive tube test for pregnancy evaluated with a selected hospital population 693
Louise Lang, M.T. (A.S.C.P.), and Alice M. Reiss, Ph.D., with the technical assistance of Linda Smith and Marcia Kerber
Hamilton, Ohio, and Raritan, New Jersey

Screening for detecting twin pregnancy 697
Madis Mägiste, M.D., Henning Von Schenck, M.D., Nils-Otto Sjöberg, M.D., Jan I. Thorell, M.D., and Anders Åberg, M.D.
Lund, Sweden

Fetus, placenta, and newborn

Nonstressed fetal heart rate monitoring in the antepartum period 699
France Rochard, M.D., Barry S. Schifrin, M.D., Francoise Goupil, M.D., Helene Legrand, M.D., Josette Blottiere, M.D., and Claude Sureau, M.D.
Paris, France, and Boston, Massachusetts

Serum levels of human placental lactogen and human chorionic gonadotropin in early pregnancy: A maturational index of the placenta 707
Louis L. Peeters, M.D., James A. Lemons, M.D., Gordon D. Niswender, Ph.D., and Frederick C. Battaglia, M.D.
Denver, Colorado

Combined obstetric and pediatric approach to prevent meconium aspiration syndrome 712
Bonita S. Carson, M.D., Rosalind W. Losey, R.N., Watson A. Bowes, Jr., M.D., and Michael A. Simmons, M.D.
Denver, Colorado

Prenatal diagnosis of placental steroid sulfatase deficiency 716
Glenn D. Braunstein, M.D., Frederick H. Ziel, B.A., Arthur Allen, M.D., Robert Van de Velde, Ph.D., and Maclyn E. Wade, M.D.
Los Angeles, California

Scalp abscess: A complication of the spiral fetal electrode 720
Craig A. Winkel, M.D., Donald L. Snyder, M.D., and John B. Schlaerth, M.D.
San Francisco, California

Current investigation

Adverse effect of amniofetography on fetal thyroid function 723
F. Rodesch, M.D., Ph.D., M. Camus, Ph.D., A. M. Ermans, M.D., Ph.D., J. Dodion, M.D., and F. Delange, M.D., Ph.D.
Brussels, Belgium

(Contents continued on page 11)



NEW & BETTER

...The all-American Frigi Colposcope

- At half the cost of comparable imports, even including the cost of teaching tube and camera adaptor.
- Superior to the finest German and Japanese models.
- Plus, choices and options to suit your practice.
- Plus sales and service representation in your locale.
- Seeing is believing. See it in your office. Call collect today.

frigitronics
OF CONNECTICUT INCORPORATED
770 RIVER ROAD, SHELTON, CONNECTICUT 06484
203/929-6321

Contents continued from page 9

Classic pages

Classic pages 727

The development of the rabbit test for pregnancy 728
Maurice H. Friedman, Ph.D., M.D.
La Jolla, California

Communications in brief

The effect of promethazine hydrochloride on fetal and maternal lymphocytes 730
John P. Gusdon, Jr., M.D., and Glenn A. Herbst, M.A.
Winston-Salem, North Carolina

Hormonal evaluation of premature menarche produced by a follicular cyst 731
Ralph G. Wieland, M.D., Rafael Bendezu, M.D.,
Marvin C. Hallberg, M.S., Peter Tang, M.D., and
Kenneth Webster, M.D.
Cleveland, Ohio

Torsion of the oviduct following laparoscopic sterilization 733
Howard I. Shapiro, M.D., F.A.C.O.G., William F. Hughes, M.D., F.A.C.S., and
Daniel H. Adler, M.D., F.A.C.O.G.
Norwalk, Connecticut

Changes in congenital oral cleft incidence in relation to induced abortions 734
Anthony P. Polednak, Ph.D., and Frank A. Oski, M.D.
Albany and Syracuse, New York

Thoracopygopagus tripus: An unusual form of conjoined twins 735
Edward M. Lichten, M.D., and Nicholas J. Teteris, M.D.
Columbus, Ohio

The prepartum diagnosis of conjoined twins by the use of diagnostic ultrasound 737
Robert L. Wilson, M.D., Curtis L. Cetrulo, M.D., and Michael S. Shaub, M.D.
Los Angeles, California

Fetal monitoring during cesarean section 738
Marian de Marinis, Leslie S. Leighton, and John W. C. Johnson, M.D.
Baltimore, Maryland

(Information for authors on page 19)

For the special needs of patients with hard, dry stools

Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT S Tablets offer comfortable relief by softening the stool *and* stimulating its movement.

Provides standardized senna concentrate, a clinically established laxative of choice
Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

Provides DSS, the classic stool softener
DSS in SENOKOT S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime SENOKOT S Tablets usually induce predictable, comfortable evacuation the next morning.

Purdue Frederick

©COPYRIGHT 1976, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856
A8339 178576

Senokot® S tablets

(standardized senna concentrate and dioctyl sodium sulfosuccinate)

the "S" stands for softener





Editors

Editors

JOHN I. BREWER, *Editor in Chief*

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, *Editors*

ALBERT B. GERBIE, *Associate Editor*

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, *Editors Emeritus*

Advisory committee on policy

David G. Anderson
John L. M. Bean
Melvin W. Breese
Tommy N. Evans
T. Terry Hayashi
Robert B. Jaffe
John Van S. Maeck
A. Cullen Richardson
J. Donald Woodruff
Samuel S. C. Yen

Board of corresponding editors

Oscar Aguero, *Caracas*
Fritz Beller, *Muenster/Westf.*
Pierre O. Hubinont, *Brussels*
Sir Norman Jeffcoate, *Liverpool*
Takashi Kobayashi, *Tokyo*

After 40 years... ...still brand new

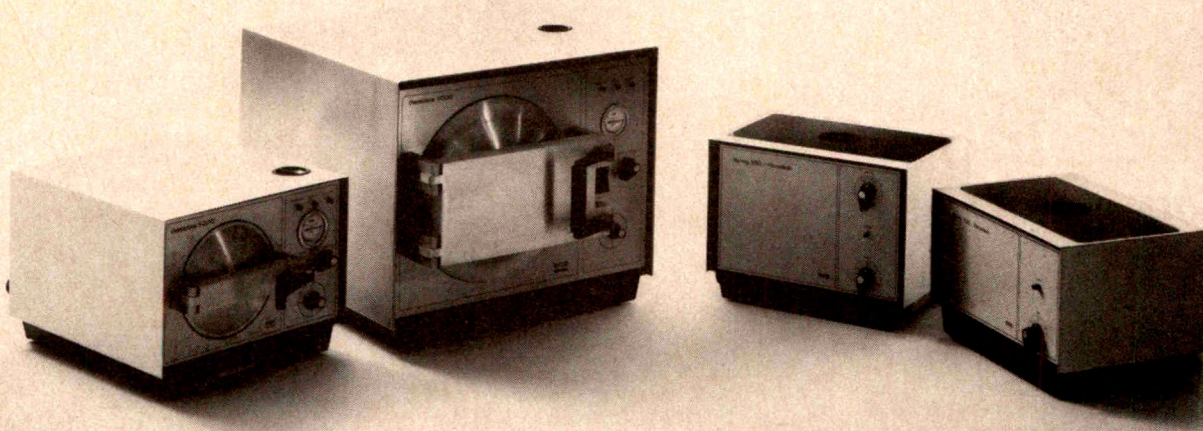
Since 1936 successive models of Harvey sterilizers and ultrasonic cleaners have represented the most advanced sterilization systems available. Today's models are no exception.

The brand new 5000 and 6000 Chemiclaves are the first fully automated Harvey sterilizers. Furthermore, they offer the shortest sterilization cycles ever... just 20 minutes.* And as with previous Harveys, Chemiclaves do not dull cutting edges, rust or corrode instruments, weaken solder joints, remove temper, or saturate or scorch soft goods. The 5000 Chemiclave is primarily for office use, while the larger 6000 Chemiclave is ideal for group practices, clinics, hospitals and institutions.

The 100 and 200 Vibracleans offer features not available on any other ultrasonic cleaners. The 200 Vibraclean even includes variable energy selection. And both models are whisper quiet. The four-quart 100 Vibraclean is large enough for most users. The six-quart 200 Vibraclean is perfect for laboratories and others who require larger capacity.

Send for our complete sterilization systems brochure. After 40 years it's still brand new.

*Exclusive of pressure rise time, which will vary.



MDT®

Chemiclave and Vibraclean are registered trademarks of MDT Corporation.

MDT CORPORATION 13618 SOUTH ALMA AVENUE GARDENA CALIFORNIA 90249 (213)321-4822

put us in your hands®


For the woman within her...
She knows her potentials, her needs for fulfillment. And she asks for your considered judgment. Put her on Ovulen, an oral contraceptive that's likely to succeed with her because its estrogen/progestogen ratio fulfills the need of most women. It's from Searle, where "the Pill" began.
Fulfills the contraceptive need of most women
Ovulen®
Each white tablet contains:
ethynodiol diacetate 1 mg./mestranol 0.1 mg.
Each pink tablet in Ovulen-28® is a placebo containing no active ingredients.
SEARLE
See next page for brief summary of prescribing information.

Actions—Ovulen® acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen depresses the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note—Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. British studies have shown an increased risk of myocardial infarction. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction or coronary thrombosis, or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding and known or suspected pregnancy.

Warnings—The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, retinal thrombosis, myocardial infarction or coronary thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and four[4-8] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while studies in the United States found relative risks of 1.9 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In one British study[9] it was estimated that users of oral contraceptives are 3 to 6 times more likely than nonusers to develop nonfatal myocardial infarction. In another British study[10] it was estimated that users of oral contraceptives between the ages of 40 and 44 were 4 to 5 times more likely to have fatal myocardial infarction than nonusers. Below the age of 40 the relative risk was estimated to be 2 to 3 times as high for users as for nonusers of oral contraceptives. The annual estimated aggregate rate of fatal plus nonfatal myocardial infarction in the 30- to 39-year age group is 4 per 100,000 in nonusers and 11 per 100,000 in users. In the 40- to 44-year age group the aggregate rates are about 22 per 100,000 and 112 per 100,000, respectively. (These estimates are based on British vital statistics, which show acute myocardial infarction death rates 2 to 3 times less than in the U.S. for women in these age groups.) The reports indicate that women with additional risk factors (hypertension, hypercholesterolemia, diabetes, cigarette-smoking, etc.) have a greater risk than the average.

In May 1974 the Royal College of General Practitioners in England[11] issued an interim report of its continuing large-scale prospective study comparing a user group with a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment. In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0. None of the American studies was designed to evaluate a difference between products. However, the Sartwell study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. Other retrospective studies[12,13] have reported an increased risk of postsurgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

Discontinue medication if there is gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[14-16] The safety of Ovulen in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect on the nursing infant cannot be determined at this time.

Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Retrospective case-control studies[17,18] have reported that women who take estrogen replacement medication to relieve symptoms of menopause may increase their risk of developing endometrial cancer by 4.5 to 13.9 times that of women who do not take these drugs. The estimated relative risks increased with duration of exposure.[17]

Although endometrial carcinoma has also been reported in young women taking oral contraceptives,[19] a statistical association has not been established.

Precautions—A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and liver function tests may be affected by treatment with Ovulen. Therefore, if such tests are abnormal in a patient taking Ovulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations, preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs Ovulen should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during Ovulen therapy.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction and coronary thrombosis, and gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding, and endometrial carcinoma.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching and vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII,VIII,IX, and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

References—1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967. **2.** Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br. Med. J. *2*:193-199 (April 27) 1968. **3.** Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br. Med. J. *2*:651-657 (June 14) 1969. **4.** Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidemiol. *90*:365-380 (Nov.) 1969. **5.** Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N. Engl. J. Med. *288*:871-878 (April 26) 1973. **6.** Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women: Associated Risk Factors, J.A.M.A. *231*:718-722 (Feb. 17) 1975. **7.** Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404 (June 23) 1973. **8.** Stolley, P. D., and others: Thrombosis with Low-Estrogen Oral Contraceptives, Am. J. Epidemiol. *102*:197-208 (Sept.) 1975. **9.** Mann, J. I.; Vessey, M. P.; Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br. Med. J. *2*:241-245 (May 3) 1975. **10.** Mann, J.I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, Br. Med. J. *2*:245-248 (May 3) 1975. **11.** Royal College of General Practitioners: Oral Contraceptives and Health, New York, Pitman Publishing Corp., May 1974. **12.** Vessey, M. P.; Doll, R.; Fairbairn, A.S., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br. Med. J. *3*:123-126 (July) 1970. **13.** Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Public Health *62*:680-685 (May) 1972. **14.** Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Health *30*:17-21 (Jan.) 1975. **15.** Janerich, D. T.; Piper, J. M., and Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N. Engl. J. Med. *291*:697-700 (Oct. 3) 1974. **16.** Carr, D.H.: Chromosome Studies in Selected Spontaneous Abortions: 1. Conception After Oral Contraceptives, Can. Med. Assoc. J. *103*:343-348 (Aug. 15 & 29) 1970. **17.** Ziel, H.K., and Finkle, W.D.: Increased Risk of Endometrial Carcinoma Among Users of Conjugated Estrogens, N. Engl. J. Med. *293*:1167-1170 (Dec. 4) 1975. **18.** Smith, D.C.; Prentice, R.; Thompson, D.J., and Herrmann, W.L.: Association of Exogenous Estrogen and Endometrial Carcinoma, N. Engl. J. Med. *293*:1164-1167 (Dec. 4) 1975. **19.** Silverberg, S.G., and Makowski, E.L.: Endometrial Carcinoma in Young Women Taking Oral Contraceptive Agents, Obstet. Gynecol. *46*:503-506 (Nov.) 1975.

Ovulen®

Each white tablet contains ethynodiol diacetate 1 mg./mestranol 0.1 mg. Each pink tablet in Ovulen-28® is a placebo, containing no active ingredients. Available in 20-, 21- and 28-pill schedules.

SEARLE **Searle & Co.** 572-R1
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co., Medical Dept., Box 5110, Chicago, Ill. 60680

American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover
the Journal is the official publication
of the following societies

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY
CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
BOSTON OBSTETRICAL SOCIETY
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SEATTLE GYNECOLOGICAL SOCIETY
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
NEW YORK GYNECOLOGICAL SOCIETY
PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION
BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SAN FRANCISCO GYNECOLOGICAL SOCIETY
JACKSON GYNECIC SOCIETY

Why make side effects part of your prescription...



recommend safe and proven conception control

Koromex products have been delivering effective spermicidal qualities for almost 50 years. They rarely have any contraindications. And, Koromex products are simple and comfortable to use. Both coil and arcing spring diaphragms are available.

Write for starter packages.

Holland-Rantos Co., Inc.

A Division of Youngs Drug Products Corp.

P.O. Box 5, Piscataway, N.J. 08854

American Journal of Obstetrics and Gynecology

Copyright © 1976 by The C. V. Mosby Company

Editors

John I. Brewer, *Editor in Chief*
303 East Superior St., Room # 222, Chicago, Illinois 60611

Frederick P. Zuspan, *Editor*
The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, *Editor*
Los Angeles County—USC Medical Center, 1240 North Mission Rd., Los Angeles, California 90033

Albert B. Gerbie, *Associate Editor*
303 East Chicago Ave., Chicago, Illinois 60611

Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

All articles published in this Journal must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority, **including all matters pertaining to human studies.** Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or publisher and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article and should conform to the style of the Cumulated Index Medicus, viz., name of author, article title, name of periodical, volume, page, and year. Authors are encouraged to limit references to *16, except* for Communications in Brief, limited to *2,* Current Investigation and Clinical Opinion, limited to *6,* and Current Developments for which there is *no* limit. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

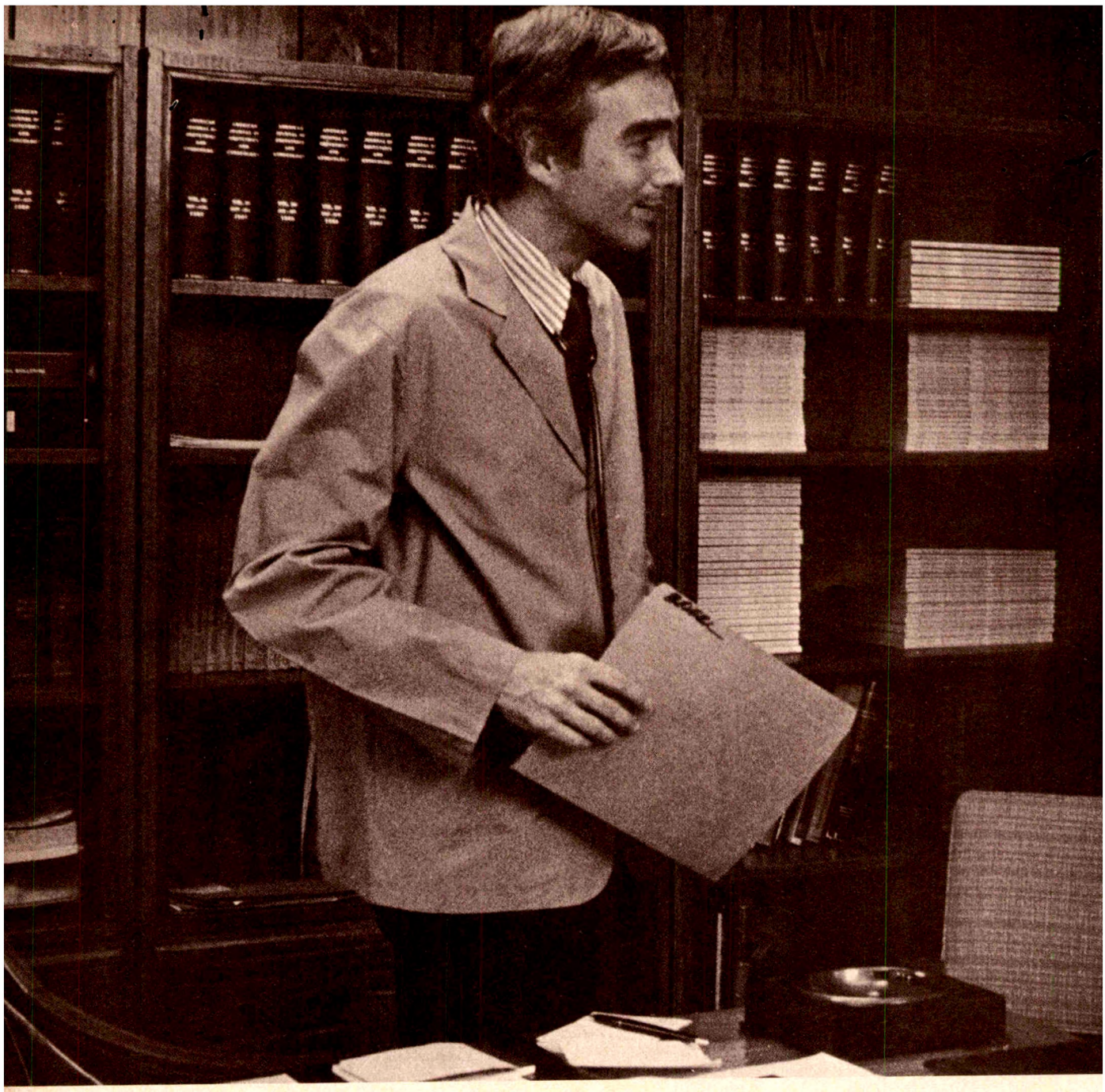
Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the Journal but may be submitted for paid advertisements, if desired.

Letters to the Editors: A brief Letter to the Editors commenting upon some article which has appeared in the Journal will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

Books. Books received will be listed in the Journal. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.



Abbott hematinics can help to provide optimum care to term

- These are the only major products containing the exact U.S. RDA* of folic acid for pregnancy—800 mcg.
- Dosage is one-a-day—helps to assure patient cooperation.
- To minimize gastric upset, each product contains 525 mg. of Ferrous Sulfate in controlled-release form—an important consideration in pregnancy.
- Both products contain 500 mg. of Vitamin C to enhance iron absorption.

*Federal Register, 38:20717, Aug. 2, 1973.



Fero-Folic-500® ℞

Controlled-Release Iron

525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption

500 mg. Ascorbic Acid (as sodium ascorbate)

Plus 800 mcg. of Folic Acid

Indications: For the treatment of iron deficiency and prevention of concomitant folic acid deficiency in non-pregnant adults. Also indicated in pregnancy for the prevention and treatment of iron deficiency and to supply a maintenance dosage of folic acid. **Contraindications:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Fero-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

Iberet-Folic-500® ℞

Controlled-Release Iron

525 mg. of Ferrous Sulfate (equivalent to 105 mg. elemental iron)

Plus Enhanced Iron Absorption

500 mg. Ascorbic Acid (as sodium ascorbate)

Plus the B-Complex

Niacinamide, 30 mg.; Calcium Pantothenate, 10 mg.; Vitamin B_1 (Thiamine Mononitrate), 6 mg.; Vitamin B_2 (Riboflavin), 6 mg.; Vitamin B_6 (Pyridoxine Hydrochloride), 5 mg.; Vitamin B_{12} (Cyanocobalamin), 25 mcg.

Plus 800 mcg. of Folic Acid

Indications: In non-pregnant adults, for the treatment of iron deficiency and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins. Also indicated in pregnancy for the prevention and treatment of iron deficiency where there is a concomitant deficient intake or increased need for B-complex vitamins (including folic acid). **Contraindication:** Pernicious anemia. **Warnings:** Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient. **Precaution:** Where anemia exists, its nature should be established and underlying causes determined. Iberet-Folic-500 contains 800 mcg. of folic acid per tablet. Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. **Adverse Reactions:** The likelihood of gastric intolerance is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. 6033133

ABBOTT





Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL* showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials

Cycle	1	12	24	36	Total Cycles 20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment. *These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

Wyeth Laboratories
Philadelphia, Pa. 19101

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Both products are available in single-cycle Pilpak® dispensers.

IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about seven-fold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

REFERENCES: 1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279, (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199, 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657, 1969. 4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am. J. Epidem. *90*:365-380, 1969. 5. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, New Eng. J. Med. *288*:871-878, 1973. 6. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J. Am. Med. Assoc. *231*:718-722, 1975. 7. Report from the Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease, and Breast Tumours, Lancet *1*:1399-1404, 1973. 8. Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners, 1974, Pitman Publishing Corp., New York, New York 10017. 9. Vessey, M.P., Doll, R., Fairbairn, A., and Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Brit. Med. J. *3*:123-126, 1970. 10. Greene, G. R., and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am. J. Pub. Hlth. *62*:680-685, 1972. 11. Nora, A. H., and Nora, J. J.: A Syndrome of Multiple Congenital Anomalies Associated with Teratogenic Exposure, Arch. Environ. Hlth. *30*:17-21, 1975. 12. Janerich, D. T., Piper, J. M., and Glebatis, D. M.: Oral Contraceptives and Congenital Limb-Reduction Defects, New Eng. J. Med. *291*:697-700, 1974. 13. Mann, J. I., and Inman, W. H. W.: Oral Contraceptives and Death from Myocardial Infarction, B. M. J., May 3, 1975, P. 245-248. 14. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, B. M. J., May 3, 1975, P. 241-245.

LO/OVRAL®

each tablet contains 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol, Wyeth

Now available...

LO/OVRAL®-28

21 white tablets each containing 0.3 mg. norgestrel with 0.03 mg. ethinyl estradiol and 7 pink inert tablets.

Wyeth Laboratories Philadelphia, Pa. 19101

American Journal of Obstetrics and Gynecology

volume 126 *number* 6 NOVEMBER 15, 1976

CLINICAL OPINION

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to six citations. Mail to Frederick P. Zuspan, M.D., Editor.

Obstetrician-gynecologists are primary physicians to women

I. Practice patterns of Michigan obstetrician-gynecologists

J. ROBERT WILLSON, M.D.

DAVID M. BURKONS, M.D.

Ann Arbor, Michigan

Michigan obstetrician-gynecologists were asked to complete questionnaires designed to determine what kinds of medical services they provide their patients. The questionnaires completed by 369 doctors, who had graduated from medical school between 1930 and 1964 and who are in active practice, form the basis of this report. More than 50 per cent treat common non-obstetric-gynecologic disorders in their own patients and smaller numbers treat more serious medical conditions. This study confirms a previous one, derived from information obtained from patients, that obstetricians-gynecologists serve as primary physicians to women, not exclusively as specialist-consultants. (AM. J. OBSTET. GYNECOL. 126: 627, 1976.)

THE ROLE of contemporary obstetrician-gynecologists is quite different from that of our specialist-consultant ancestors. The expanded services we provide are essential and appropriate, but they have changed the practice of obstetrics-gynecology completely. Each of us now has a group of women for whom we provide continuing care, often from the premarital examination through the menopause.

It is logical to assume that the patients we see regularly year after year and with whom we have established a comfortable, productive relationship might come to depend upon us for general health care. That, in fact, is what happens. In 1974, we surveyed

From the Department of Obstetrics and Gynecology, University of Michigan Medical School.

Reprint requests: Dr. J. Robert Willson, University of Michigan Medical School, Depart. of Obstetrics and Gynecology, Ann Arbor, Michigan 48104.

UNIVERSITY OF MICHIGAN 627 LIBRARY

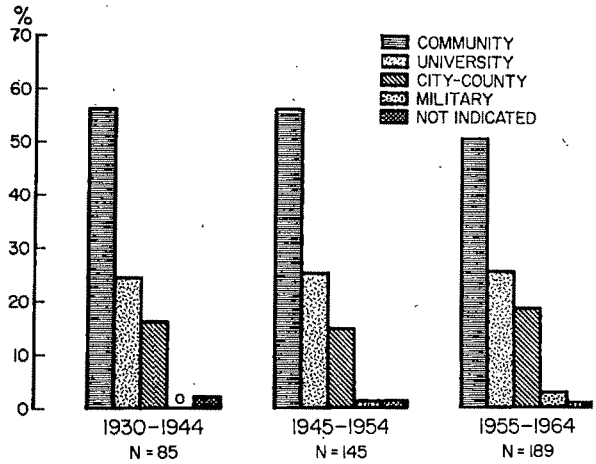


Fig. 1. Distribution of residency training according to hospital type.

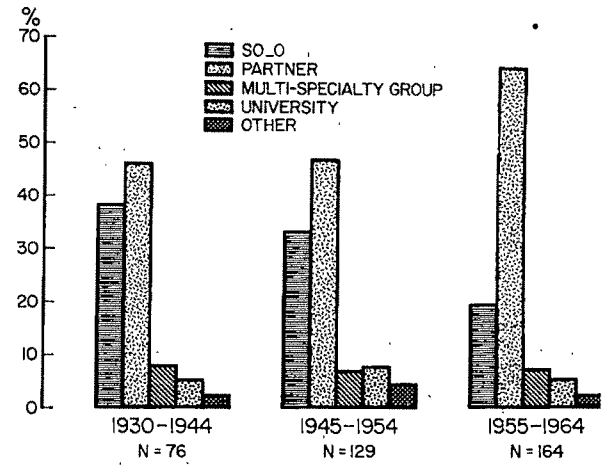


Fig. 2. Distribution according to type of practice.

1,008 patients of 51 Michigan obstetrician-gynecologists and found that 44 per cent had no physician other than their obstetrician-gynecologists and that 86 per cent see only their obstetrician-gynecologists for regular periodic examinations. Sixty-two per cent had at some time sought advice from their obstetrician-gynecologists concerning a general medical condition; 41 per cent stated that their obstetrician-gynecologists either had treated the condition or had reassured them that no treatment was necessary. A total of 256 women stated that their obstetrician-gynecologists had detected non-gynecologic conditions during periodic examinations and had either treated the conditions or referred them to other doctors.

Since so many women depend upon their obstetrician-gynecologists for periodic physical evaluation and, to a lesser extent, for general medical advice, it seemed important to learn more about the practice patterns of obstetrician-gynecologists. Consequently, we sent questionnaires to 613 Michigan Fellows and Junior Fellows of the American College of Obstetricians and Gynecologists. A total of 520 questionnaires (84.8 per cent) were completed and returned. Because we were interested in learning about the practice patterns of active, well-established obstetrician-gynecologists, we eliminated 151 from the final tabulations. Five of these had graduated from medical school prior to 1930 and undoubtedly were limiting their practices. The remaining 110 had graduated after 1965; some of these are still in training and the others, after 4 years of residency and 2 years in the military, have not been out long enough to have developed stable practices. Thirty-six more were not in active practice.

We then divided the remaining 369 practicing obstetrician-gynecologists in three groups: 76 who had been graduated from medical school between 1930 and 1944 (Group I), 129 who had been graduated between 1945 and 1954 (Group II), and 164 who had been graduated between 1955 and 1964 (Group III). This report is based upon an analysis of the questionnaires completed by these 369 physicians.

Results

Internship. Most of the respondents, 52 (68.4 per cent) of Group I, 100 (77.5 per cent) of Group II, and 127 (78.6 per cent) of Group III, had had rotating internships.

Twenty-three (30.3 per cent) of Group I, 27 (20.9 per cent) of Group II, and 34 (20.7 per cent) of Group III had had straight internships in obstetrics-gynecology. One (1.3 per cent) of Group I and one (0.7 per cent) of Group II had had straight surgical internships. One (0.7 per cent) of Group II and two (1.2 per cent) of Group III had had straight medical internships. One did not respond.

Residency. Over half of the respondents in each group had had residency training in community hospitals, and most of the remainder in university or city/county institutions. A few in Groups II and III had been trained in military hospitals (Fig. 1).

There were more responses than individuals because some in each group had been house officers in more than one hospital.

Type of practice. Twenty-nine (38.2 per cent) of obstetrician-gynecologists in Group I and 26 (33.3 per cent) of those in Group II are in solo practice, whereas only 32 (19.5 per cent) of the 1955-64 graduates practice alone. Conversely, 35 (46.1 per cent) in Group I and 61 (47 per cent) in Group II practice with other

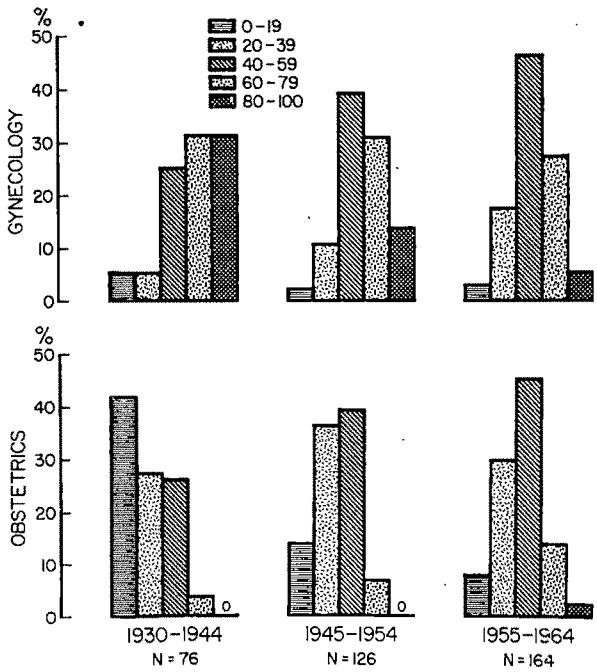


Fig. 3. Distribution of practice between obstetrics and gynecology.

obstetrician-gynecologists. In Group III, 107 (65 per cent) practice in partnerships (Fig. 2).

A few in each group practice in multispecialty group clinics, on university hospital staffs, or in other situations in which they render care on a private basis.

Distribution of effort

Obstetrics. The respondents in Groups II and III are more active in obstetrics than those in Group I (Fig. 3). It is evident that those who have been in practice the shortest period of time (Group III) devote more time to obstetrics than do those who are better established. In fact, 27 (16.4 per cent) of those who were graduated between 1955 and 1964 devote between 60 and 100 per cent of their practice time to obstetrics. Comparative figures for Group I are three (3.9 per cent) and for Group II, nine (7 per cent). It is gratifying, however, that so many of those in Groups I and II continue to do obstetrics; 23 (30.2 per cent) of the former and 60 (46 per cent) of the latter devote 40 to 79 per cent of their practice time to obstetrics.

Gynecology. The percentage of practice time devoted to gynecology has a direct relationship to years in practice. An established obstetrician-gynecologist usually does more gynecology and less obstetrics than do his younger colleagues.

This pattern holds true for Groups I and II; 68 (89.5 per cent) of the former and 109 (75.5 per cent) of the

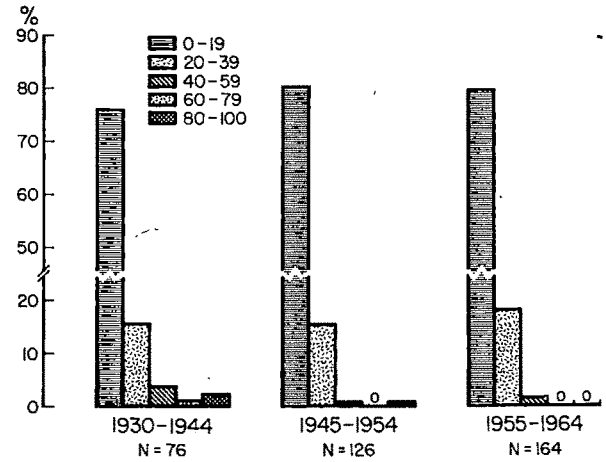


Fig. 4. Proportion of practice time spent in providing general medical care.

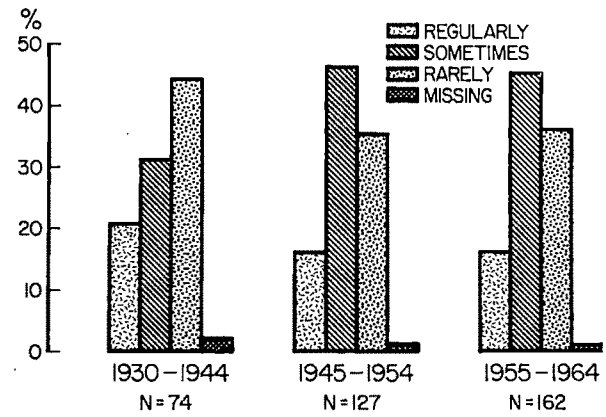


Fig. 5. Frequency of treatment of general medical conditions.

latter devote 50 to 100 per cent of their practice time to gynecology (Fig. 3). The pattern in Group III, however, is at variance with what one expects: 130 (79.2 per cent) of those graduated between 1955-64 devoted more than 50 per cent of their professional efforts to gynecology.

This may be related to differences in type of practice. A greater percentage of those in Group III practice in partnerships than do those in Groups I and II. It seems likely that many of the former entered established practices which older doctors had developed and which were already heavily weighted toward gynecology.

General medicine. The vast majority of respondents in all three groups, 58 (76.3 per cent) of Group I, 104 (80.6 per cent) of Group II, and 131 (79.9 per cent) of Group III, spend less than 20 per cent of their time providing general medical care for their patients (Fig. 4). Between 15 and 20 per cent in each group devote

Table I. Non–obstetric-gynecologic disorders treated by obstetrician-gynecologists

Disorder	1930-44 (N = 76)		1945-54 (N = 129)		1954-64 (N = 164)	
	No.	%	No.	%	No.	%
Urinary tract infections	75	98.7	125	96.9	161	98.2
Constipation	67	88.2	122	94.6	153	93.3
Marital problems	65	85.5	111	86.0	132	80.5
Backache	64	84.2	110	85.3	136	82.9
Obesity	61	80.3	102	79.0	125	76.2
Headache	58	76.3	117	90.7	143	87.8
Respiratory infections	53	69.7	107	82.9	129	78.7
Gastroenteritis	47	61.8	101	78.3	113	68.9
Minor psychiatric disorders	46	60.5	89	69.0	95	57.9
Skin lesions	43	56.6	90	69.8	110	67.1
Hypothyroidism	42	55.3	67	51.9	75	45.7
Mild hypertension	41	53.9	71	55.0	91	55.5
Gallbladder diseases	14	18.4	29	22.5	31	18.9
Moderate hypertension	13	17.1	16	12.4	20	12.2
Mild diabetes	6	8.0	30	23.3	47	28.7
Peptic ulcer disease	6	8.0	27	20.9	30	18.3
Mild heart disease	5	6.6	16	12.4	12	7.3
Hyperthyroidism	4	5.3	9	7.0	11	6.7
Major psychiatric disorders	3	3.9	2	1.6	1	0.6
Moderate diabetes	1	1.3	7	5.4	10	6.1
Severe hypertension	1	1.3	1	0.8	4	2.4
Moderate heart disease	1	1.3	0	0.0	1	0.6
Severe diabetes	0	0.0	3	2.3	5	3.0
Severe heart disease	0	0.0	1	0.8	1	0.6

between 20 and 39 per cent of their time to this endeavor and a few even more.

Forty (52.7 per cent) of Group I, 81 (62.8 per cent) of Group II, and 102 (62.2 per cent) of Group III treat non–obstetric-gynecologic conditions in their own patients regularly or sometimes (Fig. 5).

Thirty-nine (51.3 per cent) of Group I, 54 (41.9 per cent) of Group II, and 101 (61.4 per cent) of Group III treat male members of their patients' families either occasionally or regularly.

It appears that the respondents in both Groups II and III more often treat non–obstetric-gynecologic conditions than do those in Group I, and that those in Group III more often treat male members of their patients' families than do those in either other group. We anticipated that the longer obstetrician-gynecologists had been in practice, the more likely it would be that they provide more general health care for their own patients and their families. This does not appear to be true. The reason may be that the younger practitioners are having more difficulty establishing themselves as specialists because of the increasing numbers in that category and are forced to do more general medicine to survive, or that they must provide more general health care because it is not readily available in their communities.

Table II. Components of periodic examinations performed by obstetrician-gynecologists

Components	1930-44 (N = 76)		1945-54 (N = 129)		1955-64 (N = 164)	
	No.	%	No.	%	No.	%
Bimanual and speculum	76	100.0	126	97.7	164	100.0
Breasts	76	100.0	125	96.9	164	100.0
Abdomen	75	98.7	119	92.2	161	98.2
Rectal	72	94.7	118	91.5	149	90.9
Neck and thyroid	72	94.7	116	89.9	137	83.5
Heart and lungs	72	94.7	107	82.9	128	78.7
Eye, ear, nose, and throat	50	65.8	77	59.7	92	56.1
Neurologic	16	21.1	35	27.1	32	19.5
Blood pressure	76	100.0	125	96.9	161	98.2
Weight	75	98.7	123	95.3	157	95.7
Urine examination	75	98.7	113	87.6	138	84.1
Hemoglobin/ hematocrit	75	98.7	113	87.6	138	84.1
Laboratory profile	39	51.3	44	34.1	62	37.8
Chest x-ray/tuberculin test	25	32.9	35	27.1	42	25.6
Blood sugar	24	31.6	25	19.4	45	27.4

Non–obstetric-gynecologic disorders treated. The various non–obstetric-gynecologic disorders which the respondents stated they treated in their own patients are listed in order of frequency in Table I. There are no remarkable differences between the groups in kinds of disorders treated and in the percentages of obstetrician-gynecologists who treat non–obstetric-gynecologic disorders.

Periodic examination. The components of the periodic examination performed by Michigan obstetrician-gynecologists are listed in Table II. We suspect that the three members of Group II who did not check "bimanual and speculum" examination on the questionnaire overlooked it inadvertently. We are somewhat less certain about the four in the same group who did not check "breast" examination and the members of all three groups who did not check "abdominal" and "rectal" examinations.

It is obvious that most Michigan obstetrician-gynecologists do not limit their periodic appraisals to a routine pelvic examination.

Comment

Obstetrician-gynecologists have voluntarily expanded their activities to include obstetric-gynecologic services and general medical care which goes far beyond that usually available from consultants. The practices of the latter are limited to highly specialized

episodic care for patients who are referred to them by other doctors. True specialist-consultants usually provide long-term care only for those patients whose needs for special services continue. The others are returned to their primary physicians when the acute problem is resolved.

The practice patterns of specialists other than obstetrician-gynecologists, notably internists, pediatricians, and many general surgeons, also have changed. They, too, provide more general medical care than they did in the past.

The change in the practice of obstetrics-gynecology is the result of several factors. One of the most important is increasing public awareness of health care needs and increasing utilization of the preventive services, such as periodic examinations, prenatal care, contraceptive counseling, and many others, which we have made available to our patients. We now spend at least two thirds of our practice time in such endeavors. While this is important, it does represent a distinct deviation from specialist practice.

Additional reasons for the changes are the rapid expansion of our training programs and decreasing numbers of general practitioners. We have trained more obstetrician-gynecologists than are necessary to provide traditional services; hence, they have, of necessity, broadened the range of services they offer. These include many which formerly were the responsibility of the decreasing number of general practitioners.

Michigan obstetrician-gynecologists provide a considerable amount of general medical care for their own patients. Of 369 doctors in this study, 16.2 per cent treat non–obstetric-gynecologic disorders regularly and an additional 44.2 per cent treat some patients. These figures are higher than those provided by their patients, 41 per cent of whom stated that their obstetrician-gynecologists had treated them for general medical disorders.

The range of conditions for which obstetrician-gynecologists assume responsibility is wide, varying from simple urinary tract infections to the treatment of diabetes, heart disease, and hypertension and to marital counseling and the management of psychiatric disorders.

Obstetrician-gynecologists have a unique opportunity to provide a broad range of preventive and therapeutic medical care. They see their patients at regular intervals during the period of life in which many serious conditions develop. The responsibility we have assumed is indicated by the responses of 1,008 women: 86 per cent of them see no doctors other than their obstetrician-gynecologists for regular examinations. Michigan obstetrician-gynecologists do reasonably complete physical examinations and do detect unsuspected diseases; about 25 per cent of the 1,008 women reported that their obstetrician-gynecologists had discovered nongynecologic conditions during periodic examinations. The importance of performing a complete periodic examination rather than limiting the evaluation to one designed to detect cancer of the breasts and cervix is obvious: nine out of ten of our patients rely upon us alone for periodic evaluation. Certainly, we should perform complete physical examinations at least on those patients who see no other doctors from year to year.

Although obstetrician-gynecologists clearly serve in a dual capacity, that of specialist and that of primary physician to women, they are reluctant to accept the fact. In 1974, we[1] proposed that training programs be revised in an attempt to prepare house officers more appropriately for the responsibilities they will assume in practice. Our proposal provoked concern and criticism despite our describing a role for obstetrician-gynecologists of the future, which relived them of most of the routine care of normal women in order that they might add interesting and challenging medical responsibilities to the special diagnostic, therapeutic, and surgical services they now supply.

We believe the major question generated by our suggestion was whether acceptance of a role of primary physician for women might represent a giant step toward transforming obstetrician-gynecologists from specialists to general practitioners. Nothing could have been further from our minds. It is essential that obstetrician-gynecologists continue to utilize their unique skills to provide the specialized services they have in the past while they make every effort to expand and improve general health services to women.

The terms "primary physician" and "general practitioner" are not necessarily synonymous. General practitioners, the original primary physicians, see and treat patients of both sexes and of all ages, providing the general medical and surgical care of which they are capable and referring patients with problems which require unusual skills to specialists. General practitioners provide ongoing as well as episodic care for individuals and for families.

A primary physician is one who provides continuing surveillance of the medical needs of the patients for whom he accepts responsibility. He treats the acute and chronic conditions which are within his area of competence and refers his patients to appropriate specialists when their services are needed. Many primary-care physicians are specialists, internists, pediatricians, and obstetrician-gynecologists, who limit their practices much more drastically than do general practitioners.

The initial encounter between an obstetrician-gynecologist and a patient often is for premarital or prenatal examination or for contraceptive counseling. He provides whatever care is indicated and encourages her to return periodically, even though she considers herself to be well. As we see our patients year after year, it is inevitable that we will diagnose unsuspected nongynecologic disorders or that they will raise questions concerning their general health. We respond either by treating general medical conditions or by referring the patient to another physician if we cannot provide proper care. Only a few of our patients ever need gynecologic operations or medical treatment for serious disorders of reproductive function but, when the need arises, we provide the necessary specialized care. We also offer specialist-consultant services to patients who are referred to us by other doctors. Thus, by definition, we serve in a dual capacity, that of specialist obstetrician-gynecologists and that of primary physicians to women.

We will experience more changes in the future and, as is true of those which already have occurred, many of them will be of our own making. We will continue to educate obstetrician-gynecologists at at least the present rate, but our patient population will expand relatively less rapidly. This will enhance the present dilemma; there will be progressively less opportunity to develop the specialist portion of our dual role because each of us will be responsible for a smaller group of women who may ever need the specialized talents of obstetrician-gynecologists. We will probably overproduce superspecialists as we have general obstetrician-gynecologists.

We have a much better opportunity to strengthen our position than do many more limited specialties which also are overproducing. The field of obstetrics-gynecology is so broad and the needs are so great that we should have no problem in creating a challenging role for obstetrician-gynecologists in the future. If we are to accomplish this, however, we must be prepared to accept the role we now fill—that of primary physician to women—and revise our educational program appropriately.

REFERENCE

1. Burkons, D. M., and Willson, J. R.: AM. J. OBSTET. GYNECOL. **121:** 808, 1975.

The laparoscopist and electrosurgery

JOHN M. ESPOSITO, M.D.
Brooklyn, New York

A brief discussion of the physics relating to electrosurgical techniques is given, the complications inherent in this technique when used at laparoscopy are discussed, and the treatment and means of preventing these accidents are reviewed. (AM. J. OBSTET. GYNECOL. 126: 633, 1976.)

THE ADVENT of fiberoptics reopened the field of laparoscopy. Diagnostic laparoscopy was quickly embraced by the practicing gynecologist because, unlike culdoscopy, it offered a field of vision to which he was already spatially oriented. With the advancement of laparoscopy came the introduction of operative techniques, many of which depended upon the use of electrosurgical equipment.[1] It is the purpose of this paper to review the fundamentals of electrosurgery, to stress the complications which may occur, and make recommendations for proper technique.

Radio frequency current, or high-frequency current, differs from that which we use every day, at home or in the office. Home or office current is 50 to 60 c.p.s. High-frequency current, however, is in the frequency range of 100 to 5,000 kilohertz (or 1,000 c.p.s.). Experience has shown that the high frequency of these currents makes them most useful for electrosurgery. Currents of low frequency cannot be used for electrosurgery because they can cause violent muscle contractions and may also interfere with the normal conduction system of the heart.

Method

There are properties of high-frequency current which may lead to complications. These are: (1) capacitance, a property which exists between two insulated conductors, allowing high-frequency current to transverse the space between these conductors, and (2) the transmission of the current through air to other equipment.

An electrosurgical generator converts the low-frequency "office" current into high-frequency current. The generators are of two types: (1) The spark gap generator, and (2) electronic generators, that is, either vacuum tube or transistorized.

Reprint requests: Dr. John M. Esposito, Department of Obstetrics and Gynecology, The Methodist Hospital, 506 Sixth St., Brooklyn, New York 11215.

The spark-gap generator. Low-frequency current is converted to high-frequency current by the spark-gap generator. In part, this generator consists of a series of coils and capacitors which charge and discharge. The rate at which these coils and capacitors are capable of charging and discharging determines the frequency of the current. The frequencies of the currents obtained are in the area of 750 kilohertz.

Spark-gap generators were designed to have high-output voltages. These voltages are useful for superficial fulguration of lesions, transurethral resection, and coagulating bleeders which are difficult to locate. However, this same high-output voltage which is useful for these procedures has inherent disadvantages for laparoscopy. The high-output voltage causes an increase in the tendency of the current to jump to adjacent areas with resultant damage to tissues. There is also an increase in the charring capability, which can result in unwanted necrosis and secondary hemorrhage. The properties of spark-gap generator make it extremely dangerous for use in a closed-laparoscopic system. In fact, manufacturers of these units are now recommending that they not be used for operative peritoneoscopy.

Electronic generators. In these generators low-frequency currents are converted to high-frequency currents by either vacuum tubes or transistor circuitry. The high-frequency currents which they develop are in the range of 500 to 5,000 kilohertz. These generators have been designed to have a lower output voltage than the spark-gap generators. The lower voltage decreases the possibility of arcing, although it does not eliminate it completely.

The electronic currents generated are sinusoid in character, ideal for cutting; they must be modified for coagulation.

In the use of electrosurgical units there are three areas of consideration.

1. The first of these is the current available at the wall

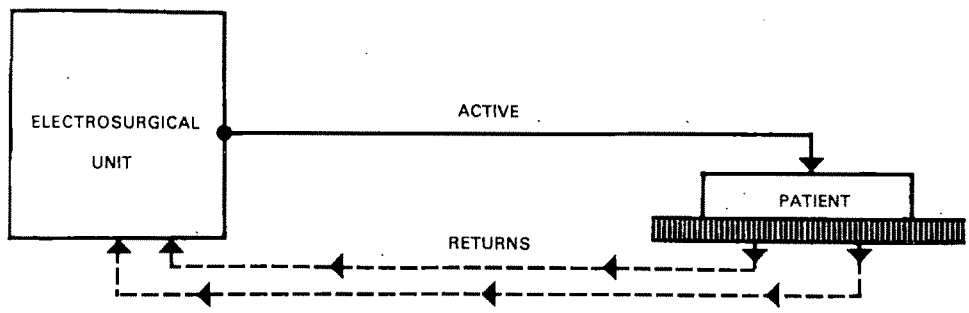


Fig. 1. Mono-terminal circuit.

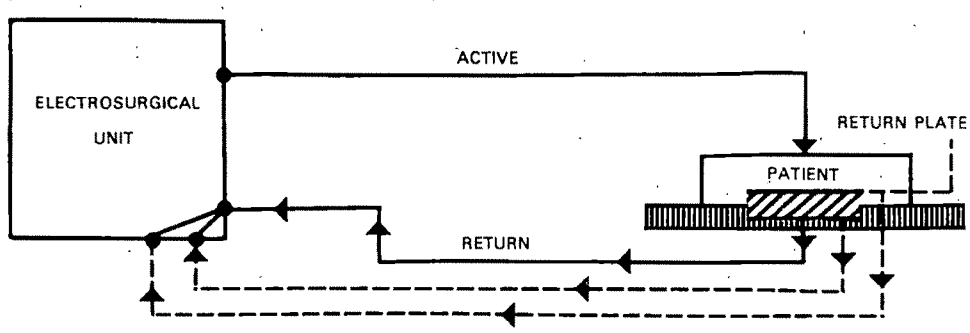


Fig. 2. Bi-terminal circuit. Note the physical connection from the electrosurgery unit cabinet to the return outlet.

outlet. In the United States, it is usually 60 c.p.s. at 120 volts. Since 60 cycle current even at low amperage is potentially dangerous, the units must be manufactured so that leakage of current to the patient or the operator is minimized.[2]

2. The second area of consideration is the electrosurgical generator itself. This is the area where the low-frequency current is converted to high-frequency current. The voltage output of the generator is dependent upon the voltage available at the wall outlet. Extreme fluctuations can cause erratic performance of the electrosurgery system.

3. The third element is the delivery/return circuit. The various configurations of these circuits are as follows.

a. Mono-terminal. As illustrated in Fig. 1, there is a single delivery from the electrosurgical unit to the patient through a cord and electrode. The return may take many paths, since there is no designated return path. This type of circuit is never used in laparoscopy.

b. Bi-terminal. As illustrated in Fig. 2, there is a single delivery from the electrosurgical unit to the patient through a cord and electrode as well as a designated return path through another cord and electrode (dispersive plate). Since a current will take the path of least resistance, most currents will return through the designated return path. As evidenced in the drawing, other paths are also available. The fact that the current could take alternate paths is both undesirable and hazardous, since shock and burns can result. To avoid this problem, manufacturers of electrosurgical units have developed isolated output units (See Fig. 3).

Notice in Fig. 3 that there is no connection between the unit cabinet and the return outlet (See Fig. 2). This effectively eliminates the possibility of the multipath return, which has been described as potentially hazardous. However, the current can still take multipaths within the patient as it seeks the return electrode. To obtain further control over the path of the current, the return electrode can be moved to the operation site in conjunction with the delivery electrode. Devices which do this are called bipolar[3, 4] (see Fig. 4).

Therefore, the bipolar system is ideal for use in laparoscopy due to the highly controlled nature of the delivery/return circuit.

Complications

A. Skin burns. Three probable causes of skin burns have been reported in the literature.[5–7]

If a unit is activated, burns can be caused by uninten-

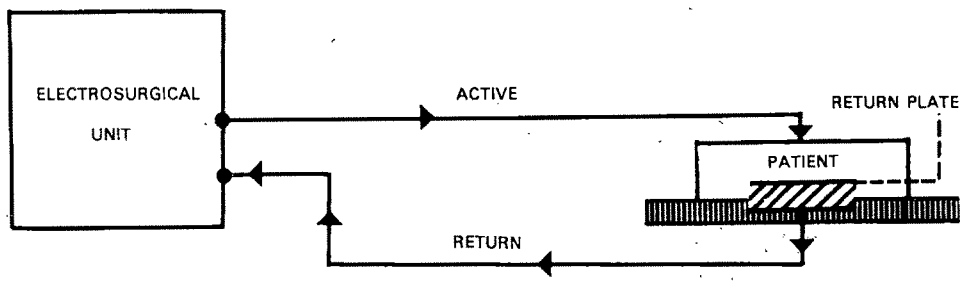


Fig. 3. Isolated output unit.

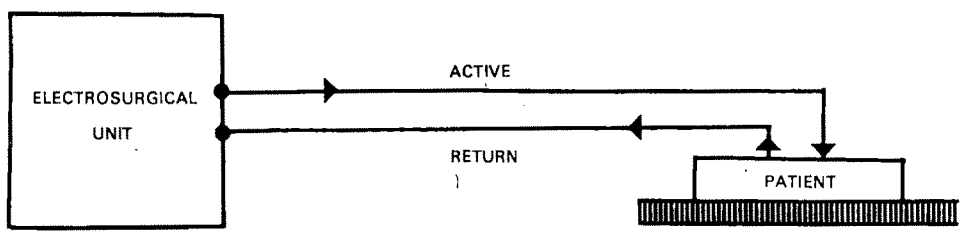


Fig. 4. Bipolar system.

tional direct contact of the electrode with the skin or by transmission through another conductive material to the skin. These situations can be avoided by[8]: (a) Not connecting the electrode to the unit until one is ready to perform the actual procedure; (b) operator control of position and activation of footswitch; (c) not placing the active electrode in contact or in close proximity to conductive material; and (d) the use of nonconductive laparoscopes and trocar sheaths.

2. Burns can be caused by alternate pathways through ground with high-current density exit points. A defect in the primary return pathway makes it necessary for the current to complete the patient circuit by alternate routes. The burn occurs at any exit point which does not provide adequate dispersion of the current. Examples of these are where skin is in contact with grounded metal or with ground electronic equipment attached to the patient, such as ECG electrodes. These accidents may be minimized by checking the continuity of the return system prior to the use of the unit. Continuity can be interrupted by a misconnection or break in the cord from the unit to the patient return electrode. Some units have a visual or auditory alarm circuit. However, it is a separate circuit and it is possible for this to be intact while the return circuit is interrupted. Therefore, it is still best to check the return electrode visually. To prevent alternate pathways, it would be ideal to have an isolated electrosurgical unit. Isolated units greatly limit the need for the current to find alternate pathways. If the continuity of the primary return path is interrupted, the current cannot find an easy alternate pathway to the ground.

3. Skin burns can be caused by poor contact between the dispersive electrode and the patient, with resultant point contacts and high current densities. Placement of the dispersive plate under bony prominences may cause uneven pressure points which could also result in burns. Bipolar electrodes would be the answer to exit burns. They limit the delivery/return circuit to the area between the bipolar elements. Such devices are now available.

Treatment of skin burns

These burns are caused by heat generated in the tissues by high-frequency currents. The initial lesion is white coagulation and its size bears no relation to the extent of the final injury.

Current flows differently in various tissues and the flow depends upon their resistance; for example, current travels farther along blood vessels. The damaged vessels undergo late degeneration and secondary anoxia causes sloughing. It is, therefore, important to wait until delineation is complete before excising the necrotic tissue.

When discovered, the lesions should be dressed with an antibiotic dressing. Prophylactic antibiotics should be administered and delineation, which takes place in approximately 72 hours, should be awaited. The area should then be excised and healing should be allowed to take place. Healing can be delayed because of the vascular damage and skin grafting may become necessary.[4]

Intestinal burns.[9–12] They may occur in one of five ways: (1) direct contact between the active electrode

and the bowel wall; (2) direct contact between the active electrode and a conductive material; (3) indirectly, by capacitance to another conductive instrument; (4) arcing; and (5) contact between the active electrode (free of current) and the bowel, before the electrode has cooled sufficiently.

In order to reduce these complications to a minimum, the following preventive measures should be taken: (a) do not attempt electrocoagulation until an adequate field of vision exists; (b) use insulated laparoscopes and trocar sheaths; (c) do not use electrosurgical units with high-arcing potential; and (d) do not step on the footswitch until the forceps are contacting the tissue.

Treatment of intestinal burns

Bowel wall burn. The injury may be discovered at the time of laparoscopy or in the postoperative period. If a high-frequency burn is recognized at laparoscopy, the initial area of blanching does not indicate the extent of damage to the bowel wall. In these cases, immediate laparotomy, followed by resection and anastomosis of the injured bowel, should be performed.

There have been cases reported in the literature of burns recognized at laparoscopy in which immediate laparotomy was not performed and in which no further surgery was necessary.[13] It is probable that these were thermal burns. We feel that if one is reasonably sure that he is dealing with a thermal burn, expectant therapy may be followed, but if the surgeon cannot be sure, the approach should be laparotomy and resection.

When injury is not recognized at surgery, symptoms usually present themselves within 72 hours, although a late reaction of as much as 6 days has been reported.[13]

These symptoms are those secondary to spillage of intestinal contents. The patient complains of abdominal pain, nausea, and vomiting. She may be febrile, have tachycardia, and present with abdominal distention, secondary to paralytic ileus. The presence of free air under the diaphragm is not diagnostic because of recent laparoscopy.

Once the diagnosis is made, there is no place for expectant therapy. As soon as the patient as been stabilized, laparotomy and resection should be performed.

Since early release after tubal electrocoagulation has become the custom, all patients should be warned to report to their physician any pain, fever, or abdominal distension. No patient who has had an electrosurgical procedure and presents with these symptoms should be ignored. If sufficient doubt exists in the mind of the physician, readmission for observation is indicated.

Urethral burn.[14] A case of unsuspected burn of the urethra was reported. The patient presented, within 72 hours, with what was thought to be massive ascites. The ascites was actually urine in the peritoneal cavity. The etiology of the injury was an unrecognized electrosurgical burn of the urethra.

The treatment is resection and reimplantation. However, this might be very difficult because of the damage to the urethral vasculature which extends well beyond the area of slough.

Abscess formation.[15] This complication has occurred in patients who have had a low-grade salpingitis at the time of surgery. The incidence is higher with electrocoagulation than cold-knife surgery because electrocoagulation produces a larger amount of necrotic tissue which is excellent pabulum for the growth of pathogenetic organism. If the diagnosis of subacute or chronic salpingitis is made at the time of laparoscopy, for tubal ligation, the electrosurgical procedure should be abandoned and the ligation should be carried by conventional methods or more extensive surgery should be performed.

Late hemorrhage. Late hemorrhage may occur from an overcoagulated portion of the Fallopian tube or from an unsuspected high-frequency burn to major pelvic vessels.

Nonpatient burns. Burns to operating room personnel also have occurred.[16] These are usually located on the hands or around the eyes. The etiology is transmission of the high-frequency current along a conductive instrument, either by direct contact with the active electrode or by capacitance. These burns may be virtually eliminated by using insulated laparoscopes and trocar sheaths, isolated output electrosurgery units, and bipolar instruments.

High-frequency interference. High-frequency currents can be transmitted through air as well as power lines. These transmitted waves may cause interference with monitoring equipment in the operating room as well as equipment in other areas of the hospital. The high-frequency interference can lead to improper diagnosis and treatment. Proper shielding of the units can help to minimize the transmission of the waves.

Electrosurgical equipment should also be used with caution in patients who have cardiac pacemakers because the transmitted waves may interfere with the pacemaker operation.[17]

Explosion and fires. We are all well aware of the dangers of this equipment in the presence of explosive anesthetic agents. However, there is a more subtle danger that lurks in the operating theater. This is the danger of igniting flammable antiseptic agents, i.e., those with an alcohol base. Aerosol sprays are particu-

larly dangerous because the propellant is flammable.[18] When an area is sprayed, the propellant remains as an invisible mist above the skin for up to 1 hour. If this were to be accidentally ignited, a flash fire could result. Therefore, as well as avoiding flammable anesthetic agents we must also avoid flammable skin preparations and aerosol sprays in patients undergoing electrosurgical procedures.

Summary

In order to decrease complications occurring during electrosurgical procedures, the following precautions should be taken.

1. The spark-gap apparatus, with its high-voltage output and high-arcing potential should be abandoned by the laparoscopist.
2. An isolated electrosurgical unit should be used if at all possible.
3. All circuitry should be checked prior to the use of the equipment.
4. Special attention should be given to the return electrode and the continuity of the circuit.
5. The dispersive electrode should be properly placed to maintain constant, good contact with the patient.
6. High-frequency leads should not be placed in the immediate vicinity of other leads that are in contact with the patient, thereby avoiding transmission of current by capacitance.
7. The return electrode should not be wet with saline or conductive gel as this may cause unstable conductivity.
8. The physician should control the footswitch at all times.
9. The active electrode should not be connected to the circuitry until one is ready to operate.
10. Nonconductive laparoscopes and trocar sheaths should be used. These should be checked periodically for defects in the insulating material.
11. The unit should not be activated unless visualization is adequate.
12. If the operator feels that the unit must be set at a higher output than usual to obtain the desired effect.
13. A bipolar electrode should be employed.
14. The equipment should be periodically inspected by trained personnel. The frequency of inspection should be determined by the amount of use to which the equipment is subjected.

The purpose of this paper has been to review briefly the physics of high-frequency electrocoagulation and to stress the complications that may occur. Suggestions have been made which will help to decrease the number of complications.

I thank Walter E. Tolles, Ph.D., for his aid in preparing the technical section of this paper. I also thank J. W. Martin, President of Cameron Miller for his technical as well as editorial advice in helping me prepare this paper.

REFERENCES

1. Palmer, R.: Essais de sterilisation tubaire coelioscopique par electrocoagulation isthmique, Bull. Fed. Soc. Nat. Gynecol. Obstet. France **14:** 298, 1962.
2. Leeming, M., Cole, R., and Howard, W. D.: Low-voltage. Direct and current burns, J. A. M. A. **214:** 1681, 1970.
3. Hulka, J. F., Thweatt, B. S., and Ulberg, L. C.: Contained cautery studies toward safer laparoscopic sterilization techniques, Fertil. Steril. **24:** 912, 1973.
4. Rioux, J. E., and Ciloutier, D.: Laparoscopic tubal sterilization sparking and control, Vie Med. Can. Fr. **2:** 760, 1973.
5. Esposito, J. M.: Electrical burns of the abdominal wall as a complication of Fallopian tube cautery, Fertil. Steril. **24:** 158, 1972.
6. Esposito, J. M.: A method for preventing abdominal burns by electrocautery during laparoscopy, Am. J. Obstet. Gynecol. **114:** 1105, 1972.
7. Thompson, B. H., and Wheeles, C. R.: Gastrointestinal complications of laparoscopic sterilization, Obstet. Gynecol. **41:** 669, 1973.
8. Battig, C. S.: Electrosurgical burn injuries and their prevention, J. A. M. A., **204:** 1025, 1968.
9. Esposito, J. M.: Letter to Editor: A method for preventing intestinal burns, Am. J. Obstet. Gynecol. **116:** 887, 1973.
10. Esposito, J. M.: Letter to Editor: A method for preventing intestinal burns, Obstet. Gynecol. **43:** 313, 1974.
11. Levinson, C. J., Schwartz, S. F., and Sallzstein, E. C.: Complication of Laparoscopic tubal cauterization small bowel perforation, Obstet. Gynecol. **41:** 253, 1973.
12. Lichter, I., Borrie, J., and Miller, W. M.: Radio frequency hazard with cardiac pacemakers, Br. Med. J. **1:** 1513, 1973.
13. Wheeles, C. R.: Out patient laparoscopic sterilization under local anesthesia, Obstet. Gynecol. **39:** 767, 1972.
14. Complications Committee of the A.A.G.L., Second Annual Report, 1973.
15. Badra, P. L., Young, J. R., Lanos, R. K., and Peterson, F. P.: Supperative salpingitis after laparoscopic tubal cauterization, Obstet. Gynecol. **42:** 511, 1973.
16. Garcia, C. R.: Electrical burns during laparoscopy, J. A. M. A., **226:** 1465, 1973.
17. Redeck, L. F.: A third degree burn secondary to faulty electrocautery ground, Anesth. Analg. **49:** 402, 1970.
18. Plumler, J. E.: Operating room flash fire from use of cautery after aerosol spray. A Case Report, Anesth. Analg. **52:** 202, 1973.

GYNECOLOGY

Plasma levels of fractionated estrogens and pituitary hormones in endometrial carcinoma

FRED BENJAMIN, M.D.
STANLEY DEUTSCH, PH.D.
Jamaica, New York

Plasma levels of estrone (E_1), estradiol-17β (E_2), and estriol (E_3), as well as follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin were measured in 30 control subjects and in 20 postmenopausal patients with adenocarcinoma of the endometrium. Within the sensitivity of the assay (5 to 10 pg.), no E_3 was found. Mean levels of E_1 and E_2 in the patients with carcinoma (42.64 ± 3.8 (S.E.M.) and 17.3 ± 1.7 (S.E.M.) pg. per milliliter) were significantly higher than those measured in the control subjects (E_1 = 26.97 ± 2.4 (S.E.M.) pg. per milliliter, $p < 0.001$; E_2 = 12.08 ± 1.2 (S.E.M.) pg. per milliliter, $p < 0.02$). Effects of age, diabetic status, and obesity were taken into consideration. Significant differences in FSH and marginally significant differences in prolactin levels were observed between the two groups. Mean levels of FSH, LH, and prolactin in the control group and the group with adenocarcinoma, respectively, were as follows: FSH = 152.3 ± 7.0 (S.E.M.) versus 98.1 ± 8.9 (S.E.M.) mI.U. per milliliter, $p < 0.001$; LH = 64.7 ± 3.1 (S.E.M.) versus 66.5 ± 5.2 mI.U. per milliliter, difference not significant; and prolactin = 14.3 ± 0.9 (S.E.M.) versus 17.8 ± 1.7 (S.E.M.) ng. per milliliter, $p < 0.06$. These results, as well as previously reported alterations in human growth hormone secretion, suggest aberrations in hypothalamic function in endometrial carcinoma. (AM. J. OBSTET. GYNECOL. 126: 638, 1976.)

FOR MANY YEARS, estrogen has been suspected as a factor in the development of endometrial carcinoma. The fact that estrogen administration can produce markedly hyperplastic endometrial patterns, indistinguishable from endometrial adenocarcinoma, as well as many other animal, clinical, and indirect studies have supported this concept.[1-3] Direct measurement of estrogens in body fluids of patients with endometrial neoplasia has been limited, until the present time, by lack of specific and sensitive methodology. Consequently, studies have yielded conflicting data. Some hormone cytologic investigations have shown increased estrogen activity,[4] while both chromatographic assays of urinary estrogens[5, 6] and fluorometric analyses[7] have been reported to be normal. Using chromatographic techniques, others have found relatively higher urinary estrogen patterns.[8] Studying conversion rates, McDonald and Siiteri[9] reported significantly increased

From the Departments of Obstetrics and Gynecology, Queens Hospital Center Affiliate of the Long Island Jewish–Hillside Medical Center, and the State University of New York at Stony Brook.

Supported by a grant (5R01 CA 13223) from the National Cancer Institute, United States Public Health Service.

Received for publication December 11, 1975.

Revised May 27, 1976.

Accepted June 18, 1976.

Reprint requests: Dr. Fred Benjamin, Queens Hospital, 82-68 164th St., Jamaica, New York 11432.

conversion of an estrogen precursor to estrone with obesity, aging, and endometrial carcinoma.

An additional problem in these investigations has been the lack of a suitable control group to which a study population can be compared. Since alleged risk factors in the development of endometrial neoplasia include age, obesity, and carbohydrate intolerance, and since the effect of these factors on plasma estrogen levels has not been adequately defined, the selection and detailed simultaneous study of an appropriate control population is essential to any meaningful investigation.

Therefore, estrogen levels, as well as the effect of age, time from menopause, obesity, and carbohydrate intolerance on these levels were studied in 30 postmenopausal control women in an effort to establish base lines for comparison with 20 patients with endometrial carcinoma.

Because of the well-known feedback mechanism between estrogens and the pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were also measured in the control group and carcinoma cases. Additionally, prolactin levels were determined because of our previous findings of alterations in another pituitary hormone, human growth hormone (hGH). In previous communications, paradoxical rises in hGH concentrations following an oral glucose load were found[10] as well as excess hGH responses to insulin-induced hypoglycemia.[11] There are several possible explanations for such hGH alterations, one being abnormal estrogen secretion and/or metabolism which has long been considered a possible factor in endometrial neoplasia. If such a relationship exists, there could be a link not only between estrogens and abnormal carbohydrate metabolism so frequently reported in those cases but also between estrogens and excess hGH secretion. There is abundant evidence that estrogens augment hGH release.

In view of these considerations, measurements of estrogen concentrations were carried out, and the levels of various pituitary hormones in patients with endometrial carcinoma were compared with those in control subjects. Because of the high and fluctuating estrogen levels in the reproductive years, and because the majority of cases of endometrial carcinoma occur after the menopause, it was decided to limit the study to postmenopausal women.

Material

Selection of subjects. Twenty subjects with histologically documented carcinoma of the endometrium were chosen for comparison with 30 normal women. All subjects in both groups were at least two years postmenopausal and had no exogenous hormone therapy for at least six months. Absence of liver, renal, and thyroid disease was ascertained by 12 parameter Sequential Multiple Analyzer profile, urinalysis, and thyroxine testing. Carbohydrate tolerance was determined by three-hour oral glucose tolerance testing after a 10 hour fast. All subjects, including patients on weight-reducing diets, were instructed to consume normal amounts of carbohydrates for at least three days prior to testing.

Efforts were made to match the control subjects and those with disease for factors which may affect endogenous estrogen levels, such as age, weight, and diabetic status. Thus, nine of 14 (64 per cent) patients with endometrial carcinoma and 20 of 30 control subjects (67 per cent) exhibited some abnormality in the glucose tolerance test according to the standards of Fajans and Conn (see Tables I and II).

Despite efforts to include overweight individuals in the control group to approximate the levels of obesity known to be associated with endometrial carcinoma, the final mean degree of obesity (28 per cent greater than "ideal" for height) is not significantly greater than the average for the American female population of postmenopausal age. Of greater importance is the significant body weight differences between the control and affected populations, 147 ± 32 (S.D.) pounds for the cancer group versus 128 ± 20 (S.D.) pounds for the control group, a difference at the 97 per cent confidence level. This will be taken into consideration by an analysis of variance of the estrogen data with respect to per cent of ideal weight between the two populations.

Methodology

Estrogen. The procedure for the radioimmunoassay (RIA) of the fractionated estrogens, estrone (E_1), estradiol-17β (E_2), and estriol (E_3), was performed according to a modified method of Wu and Lundy.[12] Because of the low levels of each estrogen present in postmenopausal women, generally in the range of less than 50 pg. per milliliter, considerable effort was devoted to an estimation of the ultimate sensitivity and reliability of the assay at these low levels, including recovery studies from serum "spiked" with each of the estrogens in the 5 to 50 pg. range. Based on these preliminary studies it can be concluded that the assays for E_1 and E_2 were able to detect an amount as small as 5 pg., with the ultimate sensitivity for E_3 being in the 10 pg. range.

The interassay variability (reliability) was determined by the measurement of an aliquot from a large plasma

Table I. Plasma E_1 and E_2 in control patients

Patient	*Age (yr.)*	*Years after menopause*	*Height*	*Weight (pounds)*	*Weight × 100 ideal body wt.*	*Diabetic status*	*E_1 ± S.D. (pg./ml.)*	*E_2 ± S.D. (pg./ml.)*
E. R.	56	5	5'4"	140	117	Normal	26.9 ± 2.2	4.7 ± 1.1
M. M.	52	2	5'1"	118	107	Normal	27.5 ± 6.3	9.1 ± 2.0
R. M.	54	15	5'4½"	145	121	Normal	36.5 ± 9.0	14.6 ± 7.1
M. B.	56	14	5'4"	110	92	Normal	3.9 ± 3.4	9.0 ± 2.4
S. F.	58	3	5'3"	159	137	Chemical	39.3 ± 9.5	34.3 ± 3.3
A. R.	57	10	4'11½"	120	114	Chemical	29.9 ± 5.7	11.4 ± 0.1
F. B.	55	8	5'1"	134	122	Chemical	21.4 ± 10.4	11.3 ± 2.3
C. A.	56	6	5'4"	160	133	Chemical	17.0 ± 4.1	7.3 ± 1.4
I. A.	61	12	5'5"	240	195	Diabetic	19.9 ± 4.4	10.1 ± 2.0
E. V.	54	2	5'3"	194	167	Diabetic	39.8 ± 7.2	10.7 ± 0.8
E. P.	56	4	5'4½"	148	123	Normal	13.1 ± 8.2	11.2 ± 1.8
A. F.	61	11	5'4"	148	123	Chemical	16.3 ± 2.3	11.5 ± 3.4
R. Ma	59	9	5'3"	126	109	Chemical	29.1 ± 5.3	9.5 ± 1.4
E. S.	64	15	5'6"	150	118	Chemical	14.3 ± 3.0	11.4 ± 3.1
H. M.	59	2	5'3"	170	147	Chemical	9.7 ± 3.5	6.3 ± 3.5
R. Mo	53	5	4'11"	120	115	Normal	33.2 ± 8.5	26.7 ± 4.5
H. G.	52	4	5'3"	152	131	Normal	8.2 ± 4.2	15.3 ± 4.3
El. P	59	7	5'2"	140	124	Normal	33.0 ± 4.8	18.4 ± 2.8
A. C.	53	8	5'1"	135	123	Normal	33.5 ± 4.3	10.5 ± 1.0
M. T.	61	12	5'3"	170	147	Chemical	35.4 ± 5.5	4.9 ± 3.9
E. Q.	68	23	5'5"	140	114	Abnormal	7.9 ± 4.3	4.1 ± 3.9
C. M.	71	–	5'0"	140	131	Chemical	54.2 ± 5.2	14.3 ± 8.0
H. C.	49	13	5'4½"	170	140	Abnormal	21.1 ± 4.9	7.5 ± 4.6
E. N.	64	5	5'5"	175	142	Chemical	35.4 ± 4.4	8.9 ± 2.4
E. O.	68	20	5'3"	180	155	Diabetic	43.2 ± 11.5	11.1 ± 0.3
F. B.	69	22	5'4"	130	108	Chemical	28.8 ± 3.0	5.2 ± 2.0
S. B.	62	15	5'3"	127	109	Chemical	49.7 ± 13.4	22.1 ± 2.7
A. C.	74	25	4'11½"	137	129	Chemical	10.7 ± 2.7	9.0 ± 1.7
E. B.	71	23	5'2"	132	117	Diabetic	43.1 ± 3.0	17.4 ± 1.1
R. S.	57	10	5'0"	145	136	Normal	27.1 ± 2.9	14.7 ± 2.1
Mean ± S.D.	60 ± 10	10.7 ± 6.9	5'3 ± 2	148 ± 28	128 ± 20		26.97 ± 13.1	12.08 ± 6.6

pool with each assay as a "quality control" sample. For E_1, all assays were ±13 per cent; for E_2, ±10 per cent.

For most patients studied, each sample was divided into 2.0 ml. aliquots for determination of estrogens (usually in quadruplicate). Plasma from control subjects and patients with adenocarcinoma was analyzed over an 18 month period with the sample selection for each assay chosen in random fashion.

In order to pool safely blood specimens taken during the three-hour oral glucose tolerance test, a few patients were evaluated for estrogen content at each of the five points of the glucose tolerance test. No significant differences were found. However, a late afternoon (seven to eight hour) specimen consistently showed significantly higher estrogen levels; therefore, these samples were not pooled or included in the data presented in this study.

Highly specific 6-carboxymethoxime antibodies were obtained from E. Kuss (Munich) and utilized for the E_2 and E_3 assays. However, for E_1, it was found that the relatively nonspecific 17-hemisuccinate–bovine serum albumin antibody* provided a more sensitive standard curve in the (low) region of interest, and this was utilized after separation of the extracted estrogens on Sephadex LH-20 microcolumns. The E_1 antibody was used at a dilution of 1:120,000; E_2 antibody, at 1:1,400; and E_3 antibody, at 1:800.

The tritiated estrogens were obtained at sufficiently high specific activities for RIA procedures* and were purified by passage through LH-20 columns prior to use. The nonspecific binding (no antibody) samples were always less than 2 per cent of the total isotope added. Recoveries to correct for procedural losses were determined by a known amount of isotopic estrogens initially added to the plasma specimens and were in the range of 60 to 80 per cent for E_1, 50 to 70 per cent for E_2, and 50 to 60 per cent for E_3.

FSH and LH. The reagents for the radioimmunoassay of FSH and LH were obtained from the National Pituitary Agency, LER-907 material being utilized as the reference standard. The biological potency of this preparation in terms of the Second International Reference Preporation of human menopausal gonadotropin, according to Midgley and Jaffe,[13] is taken as 0.046 mI.U. per nanogram for the FSH and 0.232

*Provided by I. Dyrenfurth, Columbia University.

*New England Nuclear, 575 Albany St., Boston, Massachusetts 02118.

Table II. Plasma E_1 and E_2 in endometrial cancer patients

Patient	*Age (yr.)*	*Years after menopause*	*Height*	*Weight (pounds)*	*Weight × 100 ideal body wt.*	*Diabetic status*	*E_1 ± S.D. (pg./ml.)*	*E_2 ± S.D. (pg./ml.)*
J. N.	55	5	5'4"	155	129	Chemical	26.8 ± 3.1	14.4 ± 3.5
B. L.	57	2-3	4'11"	170+	163+	Chemical	51.6 ± 4.5	19.6 ± 3.0
B. M.	80	35	5'5"	200	163	Chemical	22.3 ± 4.2	16.0 ± 6.3
C. W.	84	34	5'2"	152	135	Normal	36.4 ± 4.4	22.5 ± 2.4
P. M.	79	30	5'0"	155	145	Diabetic	46.8 ± 14.2	18.8 ± 3.8
F. G.	55	3	5'1"	205	186	Abnormal	47.0 ± 7.3	12.8 ± 2.8
L. P.	59	2	5'8"	248	184	Normal	53.3 ± 11.6	22.8 ± 2.7
A. E.	57	7	4'10"	115	113	Diabetic	37.6 ± 17.2	23.2 ± 10.4
T. S.	74	24	4'7"	115	121	Diabetic	57.0 ± 8.1	21.8 ± 6.4
M. R.	78	20	–	94	–	–	52.1 ± 27.4	13.5 (No. = 1)
Y. F.	63	5	5'3"	252	217	–	87.6 ± 13.3	27.2 ± 1.9
S. L.	58	10	5'2"	120	106	Normal	37.4 ± 7.0	12.6 ± 2.4
J. S.	59	5	–	–	–	Abnormal	50.8 ± 5.6	21.6 ± 2.7
E. R.	81	30	5'3"	130	112	–	18.5 ± 3.9	6.4 ± 2.9
I. V.	–	–	–	–	–	–	50.5 ± 5.1	20.4 ± 0.2
A. L.	56	4	5'6"	170	134	–	19.8 ± 3.6	11.7 ± 1.7
C. S.	78	35	–	–	–	–	21.4 ± 4.6	5.9 ± 5.4
C. N.	76	20	5'3"	140	121	Normal	58.3 ± 3.3	3.7 ± 1.3
M. H.	83	40	–	–	–	Chemical	47.2 ± 5.7	34.7 ± 1.0
A. C.	50	3	5'3"	190	164	Normal	30.4 ± 5.4	16.4 ± 2.3
Mean ± S.D.	67 ± 12	17 ± 14	5'2" ± 3"	163 ± 46	146.8 ± 32		42.64 ± 16.9	17.3 ± 7.5

mI.U. per nanogram for LH, and these values were utilized in the calculations. All samples, from both control subjects and patients, were analyzed in the same assay with the use of an appropriately titered sheep-rabbit globulin* for precipitation of the bound fraction. Because elevated (postmenopausal) levels were expected, and in order to utilize the most sensitive range of the standard curve, only 25 lambdas (0.025 ml.) of plasma (at least in duplicate) was analyzed for each patient.

The data from each assay, similar to the procedures for the estrogens, were processed according to a weighted least-square log-logit calculation of the standard curve values as performed on a programmable calculator.† The iodinated FSH and LH were obtained from the Serono Corp.‡

Prolactin. Serum prolactin levels were measured for all control subjects and patients in the same RIA. The pruified prolactin standard (V-L-S No. 2) and the rabbit antisera to human prolactin (V-L-S No. 1, used at a 1:20,000 dilution) were obtained from the National Institute of Arthritis, Metabolism, and Digestive Diseases. Iodinated human prolactin was provided by the Serono Corp.‡

Results

Estrogens. In approximately the first half of the women studied, in both the control group and patients, plasma E_3 was sought after but not found. Therefore, this assay was abandoned for all subsequent samples. The sensitivity of the E_3 RIA is in the range of 5 to 10 pg. Although recent reports have appeared in the literature claiming postmenopausal E_3 levels in the range of 3 to 10 pg. per milliliter, data obtained in this study do not justify the reporting of any value higher than 5 pg. per milliliter, the ultimate limit of sensitivity of the E_3 assay.

The results for E_1 and E_2 levels in the 30 control patients are shown in Table I, and those for the diseased patients are given in Table II, along with the variance around each mean value. The coefficients of variation for each sample (not shown) are generally in the range of 10 per cent for samples in the 20 to 40 pg. per milliliter range and 20 per cent for those less than 20 pg. per milliliter (for both E_1 and E_2). These variances are similar to those reported by Wu and Lundy.[12]

Comparison of E_1 and E_2 levels between the postmenopausal control and patient populations by standard Student's t test reveals statistically significantly elevated E_1 ($p < 0.001$) and E_2 ($p < 0.02$) levels. The magnitude of the mean elevation in the estrogen levels in the patients with endometrial carcinoma is 58 per cent for E_1 and 35 per cent for E_2.

Since each patient specimen was aliquoted into 2.0 ml. portions and measured in quadruplicate (four separate estrogen assays on the *same* blood sample from each patient), and since the above statistical analysis only utilizes the mean value for each patient in each group, a further test of the validity of the statistical

*Arnel Corp.
†Tektronix, Inc., P. O. Box 500, Beaverton. Oregon 97005.
‡Boston, Massachusetts.

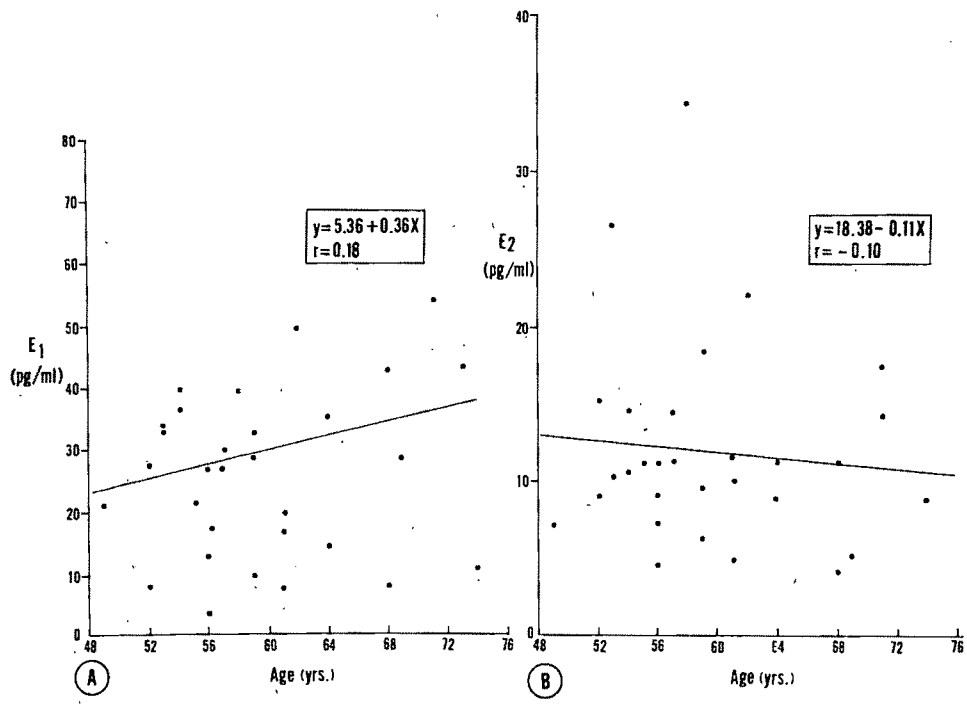


Fig. 1. *A*, E_1 levels in control postmenopausal women as a function of age. *B*, E_2 levels in control postmenopausal women as a function of age.

Table III. Student's t test analyses of E_1 and E_2 mean, median, maximum, and minimum levels for each patient in endometrial carcinoma and control populations (see text)

	E_1*			E_2*		
Value	*Control group*	*Carcinoma group*	*p*	*Control group*	*Carcinoma group*	*p*
Mean	27.0 ± 13.1	42.7 ± 16.9	<0.001	12.1 ± 6.6	17.3 ± 7.5	<0.02
Median	26.9 ± 12.8	42.7 ± 17.0	<0.001	12.2 ± 6.6	16.8 ± 7.5	<0.03
Minimum	21.6 ± 11.0	35.7 ± 15.4	<0.001	9.4 ± 6.0	14.2 ± 7.7	<0.02
Maximum	33.3 ± 15.3	49.5 ± 19.5	<0.002	15.3 ± 7.2	20.6 ± 7.6	<0.02

*All values are means ± standard deviation. There were 30 control subjects and 20 endometrial carcinoma patients.

significance of the observed differences was made by comparing the two groups according to the minimum, maximum, and median values for each subject from each group. This should provide a better indication of the intra-assay variability. These results are shown in Table III. As can be seen, while the mean values for each group change considerably, the confidence levels, as expressed by the p values, remain essentially unchanged.

Effect of age. No significant trends with age have been observed in the control population for either estrogen over the age range (49 to 74 years) of the population studied (Fig. 1). A similar lack of correlation exists in the affected group or if these data are viewed in terms of time from menopause. These results are essentially the same as a comparable analysis of data reported by others.[14]

Effect of diabetic status. As can be seen in Table IV, when patients with normal and abnormal glucose tolerance (including those with overt diabetes) are intercompared for E_1 and E_2 levels, the mean values for both groupings are quite similar, and no statistically significant differences are observed between them for either estrogen. Analysis of the data of Rader and associates[14] yields similar results, although these investigators used a combined diabetes/hypertension grouping.

However, for the control postmenopausal women with overt diabetes, the mean for E_1 is higher, but not significantly, and the possibility that a larger population may reveal significant differences cannot be ruled out from these data. This mean difference may be explicable in terms of the inordinately elevated body weights of the diabetic patients (mean of 186 versus

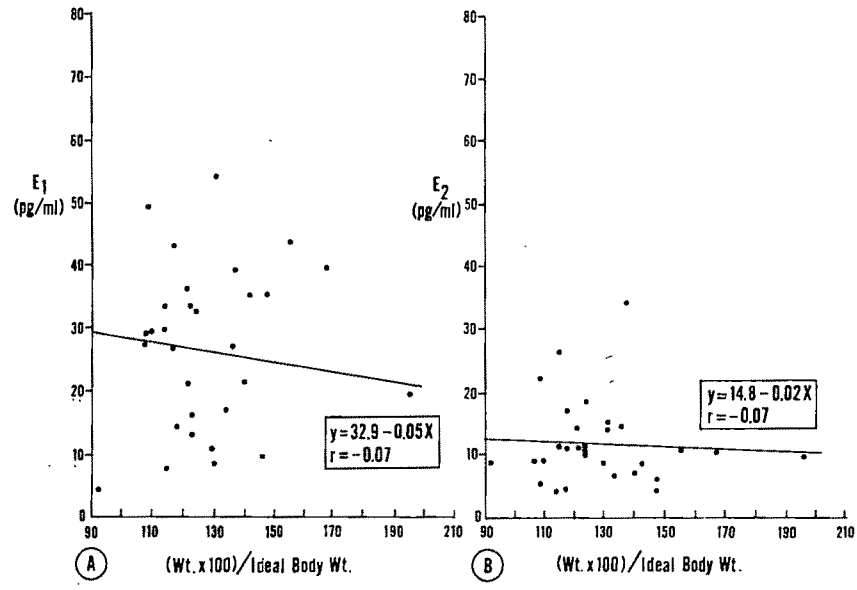


Fig. 2. *A*, E_1 levels as a function of per cent ideal body weight. *B*, E_2 levels as a function of per cent ideal body weight.

135 pounds for the normal group). Such a difference in estrogen (E_1) levels or in body weight is absent in the diabetic patients with endometrial carcinoma (Table IV). If such an increase in E_1 levels does indeed exist, it is expected that the identical proportion of patients with overt diabetes in the two populations should serve to cancel out any such effect.

Effect of obesity. The effect of the degree of obesity on the circulating levels of E_1 and E_2 in normal postmenopausal women is shown in Fig. 2. To normalize total body weight for women of differing heights, the ratio of the observed body weight to the average ideal weight for each height (×100) as obtained from insurance tables (the so-called "per cent ideal body weight") was utilized. As can be seen from the graphs, there is no significant correlation for either E_1 or E_2 levels in the weight range studied (ideal weight range = 92 to 195 per cent).

However, as shown in Fig. 3, a positive relationship between observed estrogen levels and obesity in patients with endometrial carcinoma is apparent. The cause of the differing effect between the two groups is not clear but may be related to the higher range of obesity in the diseased patients (ideal weight range = 112 to 217 per cent).

This effect, in addition to the greater average weight of the affected patients, is of crucial importance if a distinction is to be made between the role of obesity versus that of endometrial carcinoma in the observation of elevated endogenous estrogen levels.

One means of viewing these data is to compare only

Table IV. Effect of diabetic status on estrogen levels (E_1 and E_2) in postmenopausal women

Condition	*No.*	*E_1* (± S.E.M.)*	*E_2* (± S.E.M.)*
Control group			
Normal glucose tolerance test	10	24.29 ± 3.67	13.42 ± 1.93
Overt and chemical diabetes	20	28.31 ± 3.09	11.42 ± 1.53
Overt diabetes	4	36.50 ± 5.59	12.33 ± 1.93
Endometrial carcinoma patients			
Normal glucose tolerance test	5	43.16 ± 5.36	15.60 ± 3.54
Overt and chemical diabetes	9	43.01 ± 3.91	21.26 ± 2.19
Overt diabetes	3	47.13 ± 5.60	21.27 ± 1.30

*All differences are not statistically significant ($p > 0.05$).

Table V. Summary of 2 × 2 analysis of variance

Source of variation	*Degrees of freedom*	*Mean square*	*F*	*p*
A. Carcinoma or control group	1	2584.758	11.985	0.01
B. Per cent ideal weight	1	38.072	0.176	N.S.
A × B	1	416.920	1.933	N.S.
Within	42	215.654	—	
A. Carcinoma or control group	1	153.607	4.067	0.05
B. Per cent ideal weight	1	110.318	2.920	N.S.
A × B	1	131.928	3.493	N.S.
Within	42	37.768	—	

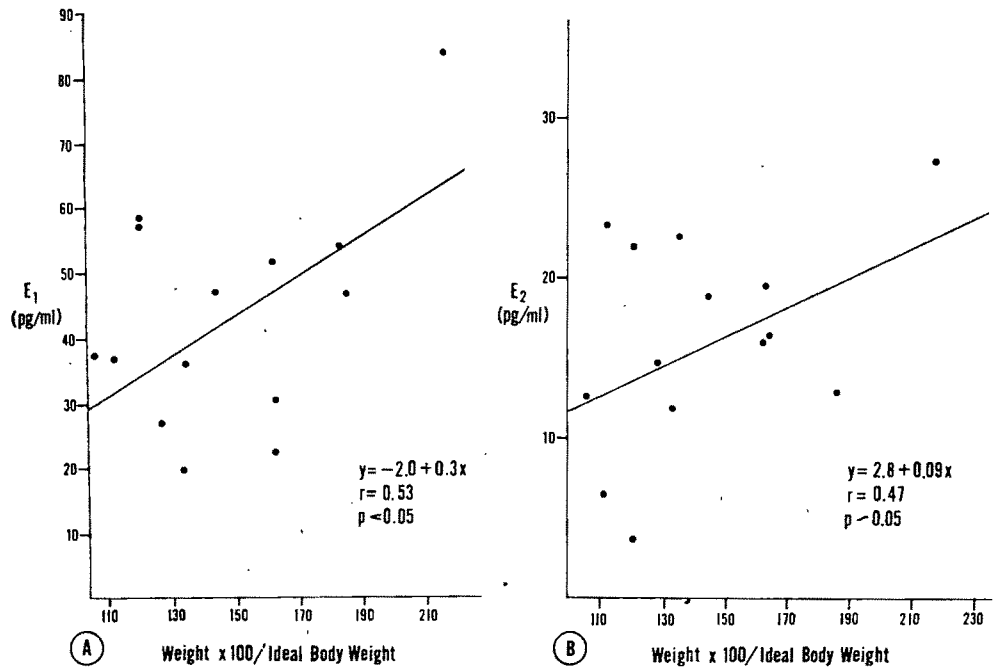


Fig. 3. *A,* Plasma E_1 levels in patients with endometrial carcinoma as a function of per cent ideal weight (see text). *B,* Plasma E_2 levels in patients with endometrial carcinoma as a function of per cent ideal weight (see text).

those patients in the two groups who exhibit comparable levels of obesity. Trial and error show that this can be done by arbitrarily selecting only those control patients with per cent ideal weight above 130 per cent for comparison with estrogen levels of all endometrial cancer patients. When this is done, the mean per cent ideal weight is virtually identical for the two groups (146.8 versus 146.2 per cent), and the respective E_1 values are for control group >130 per cent ideal weight 29.2 ± 4.1 (S.E.M.) pg. per milliliter and for all carcinoma patients 42.6 ± 3.8 (S.E.M.) pg. per milliliter, with a t test significance of $p < 0.03$. For E_2, the corresponding results are 12.1 ± 2.2 (S.E.M.) pg. per milliliter for the control group and 17.3 ± 1.7 (S.E.M.) pg. per milliliter for endometrial cancer subjects. The significance of this mean difference has been reduced ($p > 0.05$), largely because of the smaller sample population (control group = 12).

From this latter analysis, it would appear that the predominant factor in the differences in estrogen levels is not related to obesity per se, especially for the E_1 plasma levels.

A more rigorous approach is to subject these data to an analysis of variance. Such an analysis (2 × 2 factorial analysis of variance) was performed on patients and control subjects as a function of per cent ideal weight (Table V), with the data being dichotomized into those above and those below the mean per cent ideal weight. As can be seen in Table V *(A),* for both E_1 and E_2, the intercomparison of all patients versus all control subjects shows significant differences, consistent with the previous Student's t test analyses. For E_1, the variation with per cent ideal weight and the interaction between the two are significant. For E_2, a marginally significant association with obesity appears to be present* as well as an association between the pathologic state and per cent ideal weight.

FSH and LH. FSH and LH levels were measured in all control subjects and patients. The mean level of FSH in the control population is 152.3 ± 7.0 (S.E.M.) mI.U. per milliliter; that in the affected group, 98.1 ± 8.9 (S.E.M.) mI.U. per milliliter (Fig. 4). This difference is highly significant ($p < 0.001$).

No such differences were observed for the LH levels. The mean of the control group = 64.7 ± 3.1 (S.E.M.) mI.U. per milliliter, and the mean for patients with endometrial carcinoma = 66.5 ± 5.2 (S.E.M.) mI.U. per milliliter.

Prolactin. The mean value of prolactin for 30 postmenopausal control subjects was 14.3 ± 0.9 (S.E.M.) ng. per milliliter, and that for the 20 patients

*All data are analyzed with the use of a two-tailed test for significance, the null hypothesis being that there is no difference between the various groups being tested.

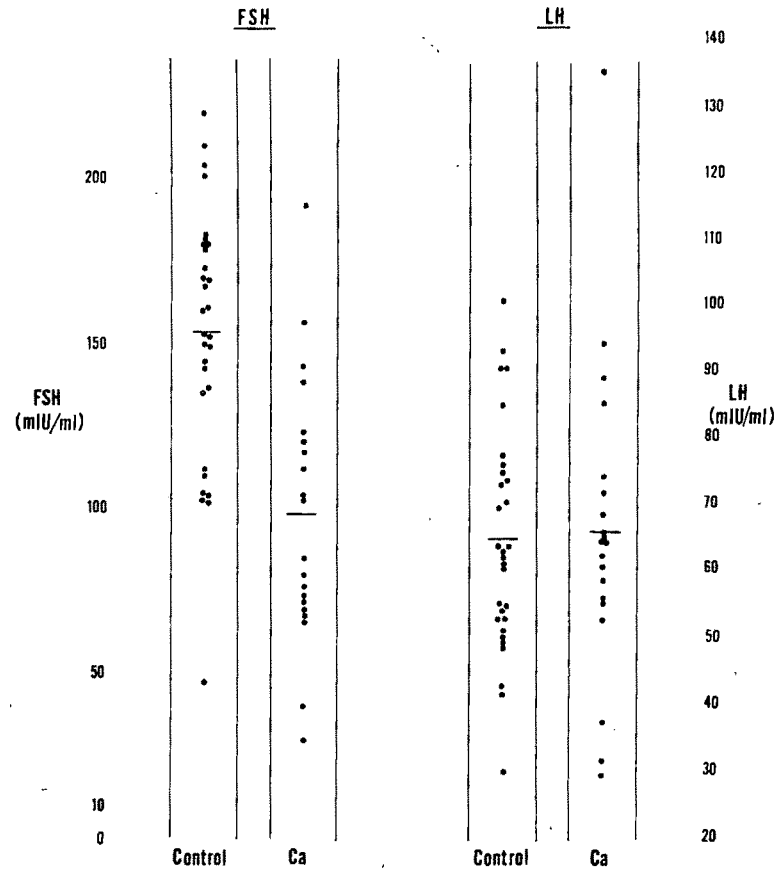


Fig. 4. Plasma FSH and LH levels in control (No. = 30) and endometrial carcinoma subjects (No. = 20). Horizontal lines are the means for each group. See text for discussion.

with endometrial carcinoma was 21.0 ± 3.6 (S.E.M.) ng. per milliliter, the difference being significant at a level of $p < 0.04$. However, one patient with endometrial cancer had a very elevated value, 81.6 ng. per milliliter. There is no justification for omitting this value from the analysis since the patient was not receiving transquilizers and did not have galactorrhea or any other known clinical state associated with elevated prolactin levels. However, if this patient is excluded, the mean value for the neoplastic patients is 17.8 ± 1.7 (S.E.M.) ng. per milliliter, and the significance of the difference is questionable ($0.05 < p < 0.06$).

Comment

This study has shown that the plasma levels of E_3 in normal postmenopausal patients and those with histologically documented adenocarcinoma of the endometrium are either absent or below the sensitivity of the assay techniques utilized (5 pg. per milliliter). Comparison of E_1 and E_2 levels between control and patient postmenopausal populations, by a standard Student's t test, has revealed statistically significantly higher mean levels of these estrogens in patients with endometrial carcinoma.

The effect of age differences in the two groups has been ruled out by this study and prior studies which have shown no correlation of circulating estrogen levels with either age or time from menopause.[14]

Elevated glucose intolerance has likewise been shown to have little effect on plasma estrogen levels. The possible influence of overt diabetes has been minimized by selection of a postmenopausal control population with a similar incidence of insulin-dependent diabetes.

An analysis of variance was utilized to assess the effect of body weight since it was not possible to obtain a control population with the degree of obesity found in the 20 patients with endometrial carcinoma. This analysis confirmed the elevated estrogen levels while showing no interaction between obesity and E_1 levels and only a weak, marginally significant interaction between obesity and plasma E_2 levels. Thus, the same conclusion may be reached, whether the intercomparison is made by selection of control subjects to provide

virtually identical body weight distributions in the two groups or by the more rigorous analysis of variance procedures.

The positive correlations, though weak, between E_1 or E_2 and degree of obesity (per cent ideal weight) found in patients with endometrial carcinoma, but not in normal control subjects are not understood but may be solely the result of the larger weight span in the patient population. That is, with our present methodology, it may not be possible to detect this effect until the body weight (and concomitant estrogen levels) is sufficiently elevated.

Because of our previous findings of elevated levels of pituitary hGH in women with endometrial carcinoma, an investigation of the gonadotropins, FSH, and LH, as well as prolactin, was deemed appropriate. A striking decrease in mean FSH levels, with no parallel change in LH levels, was found in the patients. In addition, an elevated prolactin level, though not statistically significant, was observed. More detailed studies are needed to document the presence or absence of elevated prolactin levels. The marked decrease in FSH levels is in conflict with the unreported findings of Cohen and colleagues[15] but may be consistent with the observation of Charles and co-workers[5] who, however, utilized a bioassay for total pituitary gonadotropins and found that three of nine patients with endometrial carcinoma had abnormally low urinary total gonadotropin levels. This is also consistent with the data of Dilman and associates,[7] who demonstrated substantially lowered urinary total gonadotropins (by bioassay) associated with endometrial carcinoma.

This study has now documented, with the highly specific and sensitive techniques available, the long-theorized presence of excess endogenous estrogen activity in cases of endometrial carcinoma. These higher levels may be etiologically related to the development of endometrial neoplasia and may explain our previously demonstrated excess hGH secretion in these cases. Furthermore, the excess hGH response, as well as the marked FSH suppression and moderate prolactin elevation, strongly supports the theory of hypothalamic dysfunction in this disease, as previously suggested by Dilman and associates.[7]

If it is assumed that the marked reduction observed in FSH levels in patients with endometrial carcinoma is related to the small, but significant, increments in estrone and estradiol levels, it can be hypothesized that extreme hypothalamic sensitivity exists in this disease. Evidence which may lend support to this is found in the study of Yen and colleagues[16] who observed a lesser reduction in FSH (and LH) levels in the presence of considerably higher blood estrogen levels. However, their report was based on acute exogenous administration of estrogen; therefore, its relevance to the present findings requires further investigation. Also, it is known clinically that the reduction of gonadotropin levels associated with the relief of vasomotor symptoms in normal menopausal women requires blood levels of estrogens much greater than those observed in any of the patients with endometrial carcinoma.

The relevance of these findings to the use of replacement estrogens in the perimenopausal and postmenopausal period, as well as to the rising incidence of premenopausal endometrial carcinoma and the widespread use of the estrogen-containing oral contraceptive pill, must become a source of considerable concern, particularly when the possible physiologic effect of even small increments of estrogens on the hypothalamic-pituitary axis of patients with endometrial carcinoma is noted. Furthermore, this suggested hypothalamic hypersensitivity raises the possibility that the target organ, the endometrium, may have a similar increased sensitivity, which places it at risk even to small changes in estrogen levels, from either endogenous or exogenous sources.

Indeed, there have been several recent clinical reports showing an increased incidence of endometrial carcinoma in young women using oral contraceptive pills and in menopausal and postmenopausal women receiving estrogen replacement therapy. These reports are concerned with exogenous estrogen. The present study documents the increase in endogenous estrogens and the hypothalamic dysfunction in patients with endometrial carcinoma and suggests that they may have a role in the spontaneously occurring disease.

The authors are grateful to Mr. Shiu-Hang Lai for his conscientious attention to the laboratory assays, Dr. Edwarda Rorat for the pathologic diagnoses, Drs. Nicholas Sportelli and Ira Spector for the collection of patient specimens, Dr. Vincent Fiscielli for advice on statistical analyses, and Miriam Gordon Strassfeld for editorial assistance and typing of the manuscript.

REFERENCES

1. Sherman, A. I., and Woolf, R. B.: Endocrine basis for endometrial carcinoma, AM. J. OBSTET. GYNECOL. **77:** 233, 1959.
2. Greene, J. W.: Feminizing mesenchymomas and endometrial carcinoma, AM. J. OBSTET. GYNECOL. **74:** 31, 1957.
3. Meissner, W. A., Sommers, S. C., and Sherman, G.: Endometrial hyperplasia, endometrial carcinoma and

endometriosis produced experimentally by estrogen, Cancer **10:** 500, 1957.
4. Editorial Comment, Obstet. Gynecol. Survey **20:** 849, 1965.
5. Charles, D., Bell, E. T., Loraine, J. A., and Harkness, R. A.: Endometrial carcinoma—Endocrinological and clinical studies, AM. J. OBSTET. GYNECOL. **91:** 1050, 1965.
6. Hausknecht, R. D., and Gusberg, S. D.: Estrogen metabolism in patients at high risk for endometrial carcinoma, AM. J. OBSTET. GYNECOL. **105:** 1161, 1969.
7. Dilman, V. M., Berstein, L. M., Bobrow, Y. F., Bohman, Y. U., Kovaleva, I. G., and Krylova, N. V.: Hypothalamic hyperactivity and endometrial carcinoma, AM. J. OBSTET. GYNECOL. **102:** 880, 1968.
8. DeWaard, F., Thyssen, J. H., Zeeman, W., and Sanders, P. C.: Steroid hormone excretion pattern in women with endometrial carcinoma, Cancer **22:** 988, 1968.
9. MacDonald, P. C., and Siiteri, P. K.: The relationship between the extraglandular production of estrone and the occurrence of endometrial neoplasia, Gynecol. Oncol. **2:** 259, 1974.
10. Benjamin, F., Casper, D. J., Sherman, L., and Kolodny, H. D.: Growth hormone secretion in patients with endometrial carcinoma, N. Engl. J. Med. **281:** 1448, 1969.
11. Benjamin, F.: Growth hormone secretion in patients with endometrial carcinoma, Obstet. Gynecol. **43:** 257, 1974.
12. Wu, C.-H., and Lundy, L. E.: Radioimmunoassay of plasma estrogens, Steroids **18:** 91, 1971.
13. Midgley, A. R., and Jaffe, R. B.: Regulation of human gonadotropins: X. Episodic fluctuation of LH during the menstrual cycle, J. Clin. Endocrinol. Metab. **33:** 962, 1971.
14. Rader, M. D., Glickinger, G. L., DeVilla, G. O., Jr., Mikuta, J. J., and Mikhail, G.: Plasma estrogens in postmenopausal women, AM. J. OBSTET. GYNECOL. **116:** 1069, 1973.
15. Cohen, C. J., Fogel, M., Ossowski, R., and Chen, S.-Y.: Radioimmunoassay of serum LH & FSH in postmenopausal women with endometrial cancer and postmenopausal women with diabetes; unpublished data, reported in reference 31, *in* Gusberg, S. B.: The dysfunctional and the neoplastic: Clinical investigation in the service of patient care in endometrial cancer, AM. J. OBSTET. GYNECOL. **116:** 175, 1973.
16. Yen, S. S. C., Martin, P. L., Burnier, A. M., Czekala, N. M., Greaney, M. O., Jr., and Callatine, M. R.: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17-β estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. **40:** 518, 1975.

Untreated endocervical gonorrhea and endometritis following elective abortion

RONALD T. BURKMAN, M.D.
JAMES A. TONASCIA, PH.D.
MILAGROS F. ATIENZA, M.D.
THEODORE M. KING, M.D., PH.D.
Baltimore, Maryland

A matched-pair analysis of 228 cases of endometritis occurring over a two-year period in 4,823 elective abortion patients was carried out. Patients with postabortal endometritis were matched with control subjects for age, parity, race, pay status, time of abortion, and type of abortion procedure. The prevalence of endocervical gonorrhea was 2.7 per cent in the entire group seeking abortion, with 14.7 per cent of patients with gonorrhea subsequently developing endometritis. The matched-pair analysis detected a threefold increased risk for endometritis in patients with untreated gonoccocal endocervicitis when compared with control subjects ($p < 0.05$). The significance of these findings to centers performing abortions is discussed. (AM. J. OBSTET. GYNECOL. 126: 648, 1976.)

GENITAL TRACT INFECTION, particularly endometritis, is a well-known complication of elective abortion. The occurrence of such morbidity is more frequent with midtrimester procedures than with first-trimester suction abortions and in patients of low socioeconomic status as opposed to private patients.[1] However, less well-known are other possible factors that increase such a risk.

In the presence of the current epidemic of gonorrhea, significant numbers of abortion patients may present with an asymptomatic endocervical infection. In many abortion clinics, patients are evaluated and undergo abortion prior to availability of the culture results. Whether untreated asymptomatic endocervical gonorrhea influences the subsequent development of postabortal endometritis is unknown. Therefore, the purpose of this study was to evaluate this particular problem.

From the Fertility Control Center of The Johns Hopkins Hospital, Department of Gynecology and Obstetrics and Departments of Biostatistics and Epidemiology of The Johns Hopkins School of Hygiene and Public Health.

Received for publication February 26, 1976.

Revised April 19, 1976.

Accepted May 10, 1976.

Reprint requests: Dr. Ronald T. Burkman, Women's Clinic, The Johns Hopkins Hospital, 601 N. Broadway, Baltimore, Maryland 21205.

Material and methods

From July, 1973, through June, 1975, patients in the Fertility Control Center of The Johns Hopkins Hospital who had possible postabortal endometritis were identified retrospectively. For the purpose of this study, postabortal endometritis was defined as any condition for which a patient received antibiotics within four weeks of the abortion procedure who did not have other diagnoses such as urinary tract infection listed and who were not receiving antibiotics for prophylaxis or for any other reason at the time of the procedure, as with certain cardiac patients. Patients with gonorrhea who were treated prior to or at the time of the abortion procedure were excluded.

All patients at the time of initial evaluation in the Fertility Control Center undergo culture of the endocervix for gonorrhea. During the initial six months of study, Stuart's transport media with later plating on Thayer-Martin media was used, while in the last 18 months of study specimen swabs were plated directly onto Transgrow media. All specimens were analyzed by laboratories of the State of Maryland. The diagnosis of gonorrhea was presumptively made if colonies of oxidase-positive, gram-negative diplococci grew on the media. Approximately 1 per cent of positive cultures are subjected to fluorescent antibody testing with an estimated 99 per cent agreement between these results and the culture results.[2]

Table I. Abortion procedures and endometritis cases: July, 1973, to June, 1975

Procedure	*No. of abortion procedures performed*	*No. of all endometritis cases diagnosed*	*No. of patients with endometritis hospitalized*
First-trimester	3,411	114 (3.3%)	36 (1.1%)
Second-trimester	1,412	114 (8.1%)	45 (3.2%)
Total	4,823	228 (4.7%)	81 (1.7%)

Table II. Matching characteristics

Characteristic	*No. of endometritis cases (total: 228)*	*No. of Control cases (total: 228)*
Age (years)		
≤15	21 (9.2%)	22 (9.6%)
16-20	110 (48.2%)	111 (48.7%)
21-30	87 (38.2%)	87 (38.2%)
≥31	10 (4.4%)	8 (3.5%)
Parity		
0	121 (53.1%)	121 (53.1%)
1-3	95 (41.7%)	97 (42.5%)
≥4	12 (5.2%)	10 (4.4%)
Race		
White	82 (36.0%)	80 (35.1%)
Nonwhite	146 (64.0%)	148 (64.9%)
Marital Status		
Single	159 (69.7%)	163 (71.5%)
Other	69 (30.3%)	65 (28.5%)
Pay status		
Medical assistance	97 (42.5%)	90 (39.5%)
Other	131 (57.5%)	138 (60.5%)
Procedure		
First-trimester	114 (50.0%)	114 (50.0%)
Second-trimester	114 (50.0%)	114 (50.0%)
*IUD insertion**	49 (43.0%)	58 (50.9%)
Sponge-stick curettage†	50 (43.9%)	53 (46.5%)

*First-trimester cases only.
†Second-trimester cases only.

Once postabortal endometritis was identified, patients were matched as closely as possible with control subjects from the Fertility Control Center for age, parity, race, marital status, type of pay status, time of initial intake interview, and type of abortion procedure. Also matched were intrauterine device insertions following first-trimester suction abortions and "sponge-stick" curettages required for the management of the incomplete or failed midtrimester abortion.

The data were analyzed with the use of the method of matched pairs.[3] The relative risk (RR) was the main parameter of interest since it is the ratio of the risk of endometritis in patients with endocervical gonorrhea to the risk in patients without gonorrhea. The RR was estimated as the ratio of case-control pairs discordant for the presence of gonorrhea, i.e., RR = b/c, where b is the number of matched pairs in which the case is positive for gonorrhea and the corresponding control is negative and c is the number of matched pairs in which the case is negative and the corresponding control is positive. The statistical significance of the difference in gonorrhea frequency in the cases and controls was tested with a continuity-corrected chi-square test with 1 degree of freedom: $([b - c] - 1)^2/(b + c)$. Ninety-five per cent confidence limits on the relative risk were obtained as RR × exponent

$$\left[\pm 1.96 \left(\frac{1}{a} + \frac{1}{b}\right)^{\frac{1}{2}}\right].$$

Table III. Frequency and relative risk associated with endocervical gonorrhea in patients with endometritis and control subjects

Endocervical gonorrhea status	*Cases (No. = 228)*	*Control group (No. = 228)*	*Discordant pairs**
+	19 (8.3%)	8 (3.5%)	
−	209 (91.7%)	220 (96.5%)	(17,6)

Relative risk = 17/6 = 2.8. 95 per cent Confidence limits: 1.1 to 7.2. Chi-square value (corrected for continuity) = 4.4 ($p < 0.05$).

*(b, c) Where b = pairs in which case is gonorrhea + and control is gonorrhea −; c = pairs in which case is gonorrhea − and control is gonorrhea +.

Results

During the period of study, 228 patients met the criteria used for the diagnosis of postabortal endometritis. Table I details the incidence of endometritis for first- and second-trimester abortion procedures as well as the number of cases requiring hospitalization. During the same time period, the prevalence of endocervical gonorrhea for the entire Fertility Control Center population was 2.7 per cent, with 14.7 per cent of patients with gonorrhea subsequently developing endometritis compared with 4.5 per cent for patients without gonorrhea. The rates of hospitalization for patients with the diagnosis of postabortal endometritis with endocervical gonorrhea and without gonorrhea were 36.8 per cent and 35.4 per cent, respectively. For the entire group of patients who had endocervical gonorrhea detected during the period of study, the rate of hospitalization with the diagnosis of postabortal endometritis was 5.4 per cent compared with a rate of 1.6 per cent for patients without endocervical gonorrhea.

In order to obtain the best possible estimate of any

excess risk of endometritis associated with the presence of endocervical gonorrhea, a matched control subject was selected for each patient with endometritis. Table II compares the matching characteristics of the case and control groups. All patients were matched within the month of their initial presentation to the Fertility Control Center, and most underwent the abortion procedure within two weeks of their initial evaluation. As shown, both the case and control groups were quite comparable, except that the control group of patients had undergone a larger number of intrauterine device insertions than the case group.

Table III indicates the results obtained after matching. Approximately a threefold increased risk for postabortal endometritis in patients with untreated gonococcal endocervicitis was evident when they were compared with the matched control group. The relative risk was significantly larger than 1 ($p < 0.05$) with 95 per cent confidence limits of 1.1 to 7.2

Comment

The morbidity attributable to infection following elective abortion has shown wide variability. For suction curettage completed in the first trimester, rates for "infection" or "fever" range from 0.1 to 5.2 per cent.[1, 4–7] For second-trimester procedures, most frequently intra-amniotic hypertonic saline injection, the rates have ranged from 1.5 to 18.1 per cent, depending upon the criteria used.[1, 4, 7, 8] Some studies have attempted to use objective definitions such as temperature elevation of 38° C. on two or more days. However, no universally accepted criteria for genital tract infection or endometritis exist.

Other problems are also apparent when one attempts to compare rates given in various studies. Methodology and types of patients cared for differ widely. Commonly, the follow-up of patients following abortion procedures varies from center to center. For example, in the reports reviewed, follow-up rates either were not given or ranged from 43.7 to 65 per cent.[1, 4–8]

The definition of postabortal endometritis used in this study was selected for several reasons. First, the diagnosis of endometritis cannot always be made with strictly objective criteria. Second, particularly in postabortal patients, therapeutic decisions such as the initiation of antibiotics are often made early, prior to the occurrence of events such as two or more days of fever. Finally, by exclusion of patients already receiving antibiotics or who are treated for nongenital tract infections from study, this form of bias is eliminated.

It is acknowledged that the rates of infection in this study may tend to reflect more accurately postabortion infectious morbidity. All patients in both the case and control groups had follow-up through at least the first four weeks after the procedure. All patients were seen at least once in the outpatient clinic except for 5.2 per cent of the case group and 9.7 per cent of the control group who had follow-up via direct telephone contact. In the total Fertility Control Center patient population, follow-up is obtained on about 90 per cent of patients, with approximately 75 per cent of patients followed up being examined at a return clinic visit. Also, upon discharge after the abortion procedure, patients are provided with instructions regarding potential complications. Should a complication ensue, patients are encouraged to call, and significant problems are referred directly to the on-duty physician. Through the use of this system, in the majority of instances, postabortal complications are handled directly by the physicians who perform the procedures.

The criteria used to diagnose *Neisseria gonorrhoeae* in this study were basically presumptive. As pointed out by Stafford and associates,[9] confirmatory glucose fermentation studies may lead to a significant reduction in the actual incidence of gonorrheal infections. However, as apparent from the matched-pair analysis, patients with only the presumptive diagnosis of endocervical gonorrhea are still at risk for subsequent postabortal endometritis. Furthermore, when the rates of hospitalization for patients with the diagnosis of postabortal endometritis are examined, patients with the diagnosis of endocervical gonorrhea are hospitalized more frequently than patients without gonorrhea.

The prevalence of gonorrhea of 2.7 per cent in the Fertility Control Center population is not dissimilar from the rates found in prenatal patients registering at many urban hospitals.[10] Hodgson and colleagues[5, 11] reported rates of 0.6 and 1.4 per cent in their abortion population which may reflect a different socioeconomic group of patients than seen in this study.

The matching characteristics of the case and control groups shown in Table II reveal the groups to be comparable except for an increased number of intrauterine device insertions in the control group. However, a matched-case controlled study to analyze the risk for postabortal endometritis in patients undergoing an immediate intrauterine device insertion after a first-trimester elective abortion has not indicated any increased risk for infection in such patients.[12] Therefore, this difference in number of intrauterine device insertions should not bias the study.

A potential threefold increased risk for postabortal endometritis in patients with untreated endocervical gonorrhea determined in this study indicates a need to

re-evaluate approaches to some patients requesting pregnancy termination. It has been estimated that at least one half of abortions performed in the United States are in "free-standing" clinics where both the preoperative evaluation and abortion procedure are carried out on the same day.[13] The data suggest that centers in which abortions are performed should have their rate of endocervical gonorrhea determined, and, if high, diagnosis and treatment of the disorder prior to abortion procedures should be considered. At the Fertility Control Center, attempts are being made currently to treat all patients with positive gonococcal cultures before abortion. With the use of the statistics reported in this study and the assumption that diagnosis and treatment before abortion reduce the relative risk to unity, one would expect a 68 per cent reduction in the endometritis cases among those patients with gonorrhea, although only a 6 per cent reduction in the total number of endometritis cases would be expected. However, the expected reduction in total cases increases in direct proportion to the prevalence of gonorrhea in a population. Whether such measures will significantly lower the occurrence of endometritis in such patients will require further study. If shown to be of benefit, however, many abortion clinics may have to significantly alter their policies and await gonococcal culture results before subjecting patients to abortion procedures.

Finally, of some interest was the finding that only 14.7 per cent of patients with gonorrhea develop postabortal endometritis. Despite surgical manipulation, often through the cervix, and the presence of blood and other tissue as potential culture media, it appears that either some form of protection is afforded such patients or, in this situation, *Neisseria gonorrhoeae* is of low infectivity. Salpingitis is somewhat unusual during pregnancy, perhaps due to the fact that the amniotic membrane acts as a barrier,[14] and at least one study has demonstrated the ability of cervical mucus to act as a barrier in vitro against bacteria.[15] Certainly, further definition of this "protection" would be of importance.

REFERENCES

1. Tietze, C., and Levitz, S.: Joint Program for the Study of Abortion (JPSA): Early Medical Complications of Legal Abortion, Stud. Fam. Plan. **3:** 97, 1972.
2. State of Maryland Laboratories: Personal communication.
3. Fleiss, J. L.: Statistical Methods for Rates and Proportions, New York, 1973, John Wiley & Sons, Inc.
4. Stewart, G. K., and Goldstein, P.: Medical and Surgical Complications of Therapeutic Abortions, Obstet. Gynecol. **40:** 539, 1972.
5. Hodgson, J. E., and Portmann, K. C.: Complications of 10,453 consecutive first-trimester abortions: A prospective study, AM. J. OBSTET. GYNECOL. **120:** 802, 1974.
6. Nathanson, B. N.: Ambulatory abortion: Experience with 26,000 cases (July 1, 1970 to August 1, 1971), N. Engl. J. Med. **286:** 403, 1972.
7. Evans, D. A., and Gusdon, J. P.: Medical and surgical complications of therapeutic termination of pregnancy, N. C. Med. J. **35:** 87, 1974.
8. Burnett, L. S., Wentz, A. C., and King, T. M.: Techniques of pregnancy termination: Part II, Obstet. Gynecol. Survey **29:** 6, 1974.
9. Stafford, R. H., Ansbacher, A., Otterson, W. N., and Plunkett, G. P.: Gonorrhea among females in a military population, Obstet. Gynecol., **42:** 33, 1973.
10. Spence, M. R.: Gonorrhea in a military prenatal population, Obstet. Gynecol. **42:** 223, 1973.
11. Hodgson, J. E., Major, B., Portmann, R., and Quattlebaum, F. W.: Prophylactic use of tetracycline for first trimester abortions, Obstet. Gynecol. **45:** 574, 1975.
12. Burkman, R. T., and Tonascia, J. A.: Unpublished data.
13. Weinstock, E., et al.: Legal abortions in the United States since the 1973 Supreme Court Decisions, Fam. Plann. Perspect. **7:** 23, 1975.
14. Acosta, A. A., Mabray, C. R., and Kaufman, R. H.: Intrauterine pregnancy and coexistent inflammatory disease, Obstet. Gynecol. **37:** 282, 1971.
15. Enhörning, G., Huldt, L., and Melen, B.: Ability of cervical mucus to act as a barrier against bacteria, AM. J. OBSTET. GYNECOL. **108:** 532, 1970.

Amylases of the genital tract

I. Isoamylases of genital tract tissue homogenates and peritoneal fluid

G. SKUDE, M.D.
P. A. MÅRDH, M.D.
L. WESTRÖM, M.D.
Malmö and Lund, Sweden

Homogenates of tissue from the female genital tract contain isoamylases which are, to a certain extent, electrophoretically distinguishable from the pancreatic and salivary isoamylases. In healthy nonpregnant women, high levels of activity of genital isoamylases were found in tissue homogenates of cervical and Fallopian tube mucosa, whereas activity was weak or absent in homogenates of endometrium. The isoamylases of the cervical mucosa had an electrophoretic migration rate toward the anode identical to that of the salivary main fraction, whereas the isoamylases of the Fallopian tube migrated faster. Specific genital isoamylase activities were also demonstrable in peritoneal fluid collected from the cul-de-sac. During the menstrual cycle, these activities showed a midcycle peak. In pregnant women, the levels of activity of the genital isoamylases in peritoneal fluid were lower than in nonpregnant women. In homogenates of the male accessory genital glands, the isoamylases specific for the genital tract were present in minute amounts. The isoamylases specific for the genital tract were not detectable in serum in either sex.
(AM. J. OBSTET. GYNECOL. 126: 652, 1976.)

THE AMYLASE ACTIVITY in serum is derived from the pancreatic and salivary glands.[1] That there is local production of amylase in the epithelium of the human genital tract is deduced from observations of high levels of amylase activity in the contents of cysts derived from the Müllerian or mesonephric duct.[2-5] In human subjects as well as in some animal species, i.e., cow, sheep, and golden Syrian hamster, the concentration of amylase in homogenates of the uterine tubes is high. In some species, i.e., dog, cat, rat, mouse, and guinea pig, no evidence of tubal amylase production is found, at least not during estrus.[6, 7]

The present report describes the patterns of the isoamylases found in tissue homogenates of various parts of the female and male genital tracts as well as the isoamylase pattern in peritoneal fluid obtained from the cul-de-sac of nonpregnant and pregnant women.

From the Department of Clinical Chemistry, University of Lund, Malmö General Hospital, Malmö, the Institute of Medical Microbiology, University of Lund, and the Department of Obstetrics and Gynecology, University Hospital, Lund.

Supported by grants from the Swedish Medical Research Council (Projects Nos. B76-13X-581-12B and B76-16X-04509).

Received for publication February 4, 1976.

Accepted May 19, 1976.

Reprint requests: Dr. L. Weström, Department of Obstetrics and Gynecology, University of Lund, S-221 85 Lund, Sweden.

Clinical material and specimen collection

Tissue specimen.

Fallopian tubes. One or both Fallopian tubes were obtained from 14 women. Five of them, between 25 and 35 years of age, underwent legal sterilization for nonmedical reasons. With the patient's consent, the operation was performed as a salpingectomy. Uterine tubes were obtained at hysterectomy from seven women between 35 and 45 years old. These seven women were still menstruating. Tubes from one postmenopausal woman were obtained at hysterectomy. From one pregnant patient, in the twentieth week of gestation, the tubes were removed and the pregnancy was interrupted because of diabetes mellitus. With the exception of this woman, who was treated with insulin, and three women who were using oral contraceptives, neither hormonal nor radiologic treatment was given to any of the women before operation. Malignancy was not found in any of the specimens removed at operation.

Endometrium. This was obtained from hysterectomy specimens of three of the women of child bearing age. Decidual tissue was obtained from the pregnant diabetic woman.

Cervical mucosa. Mucosa was obtained from the above-mentioned three hysterectomy specimens.

Urinary bladder mucosa, prostatic gland, prostatic utricle, and seminal vesicles. Specimens from these structures were obtained from one male subject, operated upon because of carcinoma of the urinary bladder.

Peritoneal fluid. Peritoneal fluid from the cul-de-sac was collected at laparoscopy from 15 women, between 19 and 34 years old. The laparoscopy was performed as part of an investigation of infertility in five women and because of acute abdominal pain, which laparoscopy revealed to be ovulatory, in 10 women. All 15 women had normal internal genital organs and were menstruating regularly. The peritoneal fluid was aspirated by means of a cannula which was introduced into the abdominal cavity through a separate incision in the abdominal wall. Peritoneal fluid was also obtained from the cul-de-sac of six pregnant women in the eighth to twelfth gestational weeks who were undergoing legal abortion. These samples were collected by a needle puncture of the cul-de-sac through the posterior vaginal fornix.

Serum samples. A blood specimen was drawn at operation from all subjects.

Laboratory methods

Tissue homogenates. After careful rinsing in 0.9 per cent sodium chloride, the tissue specimens were homogenized with a tissue homogenizer* in 0.025M phosphate buffer, pH 7.0, containing 0.9 per cent sodium chloride. The homogenates then underwent sonication. The clear supernatant obtained after centrifugation at 4,000 g for 15 minutes was used for electrophoretic analysis.

Organ cultures. Specimens from the tubal isthmus, ampulla, and fimbria of three of the Fallopian tubes removed at operation were maintained as organ cultures.[8] Minimum essential medium† (MEM) was used without further addition for the transportation of the specimens and as organ culture medium. The organ cultures were set up in Petri dishes. The tissue pieces were nailed to silicone rubber disks. Incubation was made in 10 per cent carbon dioxide at 37° C.[8] The isoamylases were studied in the medium used to transport the tubes and in the organ culture medium after one, two, three, and five days of incubation, at which intervals half of the medium in the Petri dishes was replaced. At the end of the culture maintenance period, the tissue samples were homogenized, and their isoamylase patterns were determined.

Amylase determinations. The total amylase activity was determined with the Phadebas amylase test.* Agarose gel electrophoresis was used to separate the various isoamylases.[9]

The isoenzyme patterns of the corresponding serum and peritoneal fluid samples were visually compared, and the contribution of the genital tract isoamylases was determined. The judgment was based on the staining intensity on the anodal side of the salivary main fraction of the peritoneal fluid samples, compared with that of serum (Fig. 1). The contributions of the individual groups of isoamylases to the total amylase activity of serum and peritoneal fluid collected from the cul-de-sac were also determined by densitometric scanning.

Evidence of amylase identity. To ascertain the amylase identity of the starch-degrading enzyme produced by the specimens studied, 100 μl of each homogenate or peritoneal fluid specimen to be tested was mixed with 5 μl of rabbit anti-human parotid amylase. After incubation for 30 minutes at room temperature, the mixture was centrifuged, and the supernatant was used for electrophoretic separation.

Results

Tissue homogenates.

Fallopian tube. As exemplified by Sample 2 (Fig. 1), the specific isoamylases from the Fallopian tube specimens consisted of one main fraction whose migration rate toward the anode was faster than that of the salivary main fraction. In addition to this genital main fraction, there were two weak fractions—one with a mobility equal to that of the salivery main fraction and one which migrated even faster than the genital main fraction. No difference was observed with respect to isoamylase patterns between homogenates from different parts of the tubes. A different Fallopian tube isoamylase pattern is shown as Sample 3 (Fig. 1). In this case, the fraction showing the most pronounced enzyme activity had a still higher migration rate toward the anode. In addition, in this specimen, there was one more enzyme component on the anodal side of the genital main fraction. In homogenates from the uterine tubes obtained from the pregnant woman, no specific genital isoamylase activity could be demonstrated.

Endometrium. In homogenates from the endometrium from the main part of the uterine corpus, no

*Turnex.

†Flow Laboratories Ltd., England.

*Pharmacia, Uppsala, Sweden.

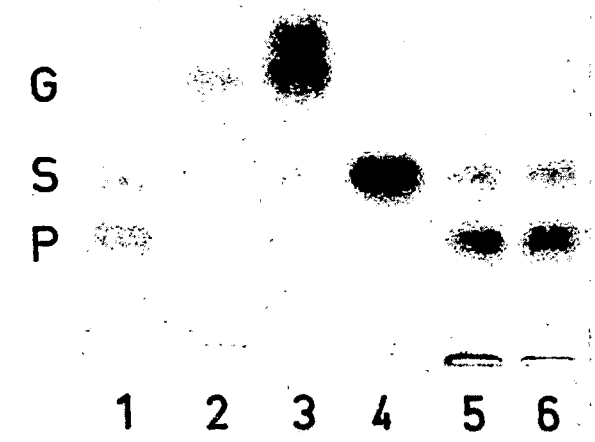


Fig. 1. Isoamylase patterns of serum and tissue homogenates from the genital tract. *P* denotes main pancreatic isoamylase fraction; *S*, main salivary fraction; *G*, genital tract isoamylase. The anode is above. Sample 1: Normal serum. Sample 2: Fallopian tube homogenate. Sample 3: Fallopian tube homogenate. Sample 4: Cervical mucosa homogenate. Sample 5: Prostatic gland homogenate. Sample 6: Seminal vesicle homogenate.

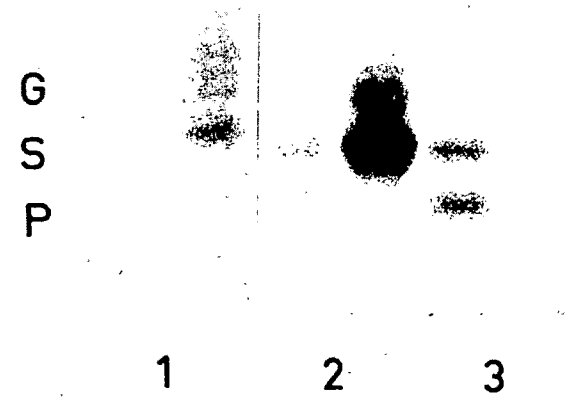


Fig. 2. Typical isoamylase patterns of serum (left) and peritoneal fluid (right). For abbreviations, see legend to Fig. 1. Sample pair 1: Nonpregnant woman. Two genital tract–specific fractions in peritoneal fluid not detectable in serum. Sample 2: Nonpregnant woman. One genital tract–specific fraction in peritoneal fluid not detectable in serum. Sample 3: Nonpregnant woman. Additional fast-migrating salivary isoamylase fractions detectable in serum.

Table I. Mean values and ranges of the isoamylase activities (units per liter) in serum from 15 nonpregnant and six pregnant women

	Nonpregnant women		*Pregnant women*	
Isoamylase	*Mean*	*Range*	*Mean*	*Range*
Pancreatic	90	40-160	72	40-120
Salivary	73	40-110	72	40-110
Total	163	90-260	143	80-230

Table II. Mean values and ranges of the isoamylase activities (units per liter) in peritoneal fluid from 15 nonpregnant and six pregnant women

	Nonpregnant women		*Pregnant women*	
Isoamylase	*Mean*	*Range*	*Mean*	*Range*
Pancreatic	40	10-115	32	10-70
Nonpancreatic	306	115-670	121	50-250
Total	345	210-700	152	60-290

specific isoamylase activity could be detected. Very weak activity was observed in some homogenates of endometrium obtained from areas close to the uterine orifices of the Fallopian tubes. In homogenates from decidua obtained in the twentieth gestational week from the patient with diabetes mellitus, no specific isoamylase activity was demonstrable.

Cervical mucosa. In homogenates of cervical mucosa from all three patients investigated, the isoamylase pattern was characterized by one prominent main fraction corresponding to the slowest migrating satellite fraction of the tubal samples, i.e., a migration rate corresponding to the salivary main isoamylase fraction (Sample 4, Fig. 1). In front of the cervical main fraction, a weak zone of amylase activity was detectable.

Specimens from the male genital tract. A very weak zone of amylase activity, corresponding in mobility to the main specific genital fraction in homogenates of Fallopian tubes, could be identified in the homogenates of prostatic tissue and possibly also in homogenates of the seminal vesicles. In homogenates of the other structures of the male genital tract, i.e., bladder mucosa and prostatic utricle, no specific genital isoamylase activity could be demonstrated (Samples 5 and 6, Fig. 1).

Organ culture specimens. The total amylase activity and the specific genital isoamylase patterns were identical in homogenates of Fallopian tube specimens analyzed immediately after removal from the patient and in specimens after five days in organ culture. The corresponding activities and patterns in media collected on different occasions during maintenance of the organ cultures were likewise identical, i.e., show-

ing the specific genital isoamylase pattern of the Fallopian tubes. In fresh MEM, no amylase activity was detectable.

Serum. The mean values and ranges of the isoamylase activity in serum from the nonpregnant and pregnant women are given in Table I. The specific genital isoamylases seen in homogenates of tissue from the Fallopian tubes as well as in the peritoneal fluid were not detectable in serum. Due to genetic variations, some additional fast-migrating salivary fractions were seen in serum from some women (Sample 3, Fig. 2).

Peritoneal fluid. The pattern of the level of isoamylase activity in the peritoneal fluid of healthy nonpregnant women was characterized by the pancreatic main fraction, the salivary main component migrating together with one of the genital tract isoamylases, which gave this fraction a higher level of enzyme activity than that of the corresponding fraction in the serum samples, and, in front of this combined salivary and genital isoamylase fraction, two (Sample 1, Fig. 1) or one (Sample 2, Fig. 2) additional broad fraction having rather diffuse margins. Due to genetic variations of the salivary isoamylases, some women demonstrated additional fast-migrating salivary isoamylase fractions in both serum and peritoneal fluid samples (Sample 3, Fig. 2). These fast-migrating salivary isoamylase fractions were always very narrow and distinct and were easily distinguishable from the genital tract isoamylases. In the peritoneal fluid of healthy nonpregnant women, the total level of amylase activity was more than twice that of serum (Table II). As it was not possible to distinguish all of the isoamylase fractions of genital origin from those of the salivary glands, the sums of the activities of these two groups of isoamylases were determined in the peritoneal fluid specimens. The mean *nonpancreatic* isoamylase activity accounted for more than 85 per cent of the total activity in nonpregnant women (Table II).

Visual estimation of the contribution to the peritoneal fluid of the isoamylases from the genital tract revealed their presence in all nonpregnant women studied. In the pregnant women, the specific genital isoamylase activities were considerably reduced or even absent.

The quotient between nonpancreatic isoamylase activity in fluid from the cul-de-sac and that in serum, which can be regarded as a measure of the genital isoamylase contribution to the fluid in the cul-de-sac, varied in healthy nonpregnant women between 1.5 and 16.4 (mean 4.8). The quotients were about two in the early and late stages of the menstrual cycle but reached higher values (more than 15) around the estimated time of ovulation. Apart from this ovulatory peak, there were no differences in the pattern of the isoamylases in peritoneal fluid between women who used oral contraceptives or intrauterine devices and those who did not use any contraceptives.

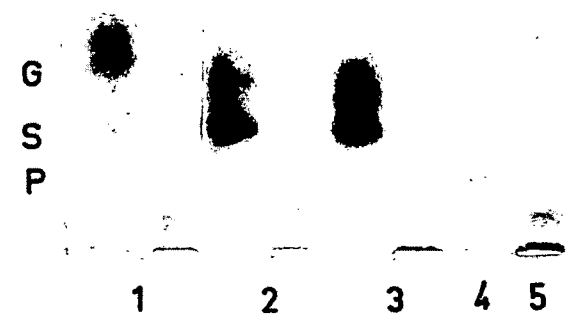


Fig. 3. Change in isoamylase pattern after addition of anti-amylase. For abbreviations, see legend to Fig. 1. Sample pair 1: Tubal homogenate before (left) and after (right) the addition of anti-amylase; Samples 2 and 3 are from the cul-de-sac before and after addition of anti-amylase. Sample 4: Normal human serum without anti-amylase. Sample 5: Rabbit antiserum diluted in sodium chloride solution.

In the pregnant women, the peritoneal fluid/serum nonpancreatic isoamylase activity quotient varied between 0.6 and 2.2 (mean 1.55).

Evidence of amylase identity. The addition of anti-amylase to the tissue homogenates and the specimens from the cul-de-sac completely abolished the salivary and pancreatic isoamylase activities as well as the additional starch hydrolyzing activity found in the samples from the female genital tract (Sample pairs 1 to 3, Fig. 3).

Comment

The present study confirms earlier reports[2–5] on a local production of enzymes with activity in organs derived from the Müllerian ducts and mesonephron. In healthy nonpregnant women, specific genital isoamylases were demonstrable in tissue homogenates of Fallopian tube and cervical mucosa but not endometrium. The isoamylases of the cervical mucosa had an electrophoretic migration rate identical to that of the salivary main fraction, whereas the isoamylases of the Fallopian tubes generally migrated faster toward the anode.

The facts that different parts of the female genital tract show different specific genital isoamylase activities

and patterns and that culture media of Fallopian tube organ cultures show no decrease in isoamylase activity with time, despite the fact that half the volume of the media was changed daily, strongly suggests that production of the specific genital isoamylases is local. The particular cells responsible for this local enzyme production are not yet known.

The amount of isoamylase produced in the genital organs is small compared to that produced by the pancreatic and salivary glands. No isoamylase activity corresponding to that found in tissue homogenates of the Fallopian tube could be detected in serum.

"Leakage" of enzymes from the Fallopian tubes into the peritoneal cavity is likely, as specific genital isoamylases were identified in peritoneal fluid from the cul-de-sac. The isoamylase pattern of this fluid reflects that of the tissue homogenates of Fallopian tubes, although some of the weaker fractions of the specific genital isoamylases found in tissue homogenates were not detectable in peritoneal fluid. Peritoneal fluid may be used for the analysis of variation in specific genital isoamylase activities. Such variations were noted during the menstrual cycle, the specific genital isoamylase activities showing a peak activity around the estimated time of ovulation. It was also noted that the activities were low or absent during an intrauterine pregnancy.. Studies of isoamylase activities in peritoneal fluid have also been made in patients with infections of the Fallopian tubes[10] and in those with ectopic pregnancy.

In the male subject, genital isoamylase activity was found in the tissue homogenates of the prostate and seminal vesicles. However, the isoamylases were produced in amounts so minute that they could not be detected in seminal plasma.[2]

The biological significance of the isoamylases in the female genital tract is not known. The demonstrated variations of the specific genital isoamylases during the menstrual cycle suggest a role of these enzymes in the physiologic processes of reproduction.

REFERENCES

1. Meites, S., and Rogols, S.: Amylase isoenzymes, CRC Crit. Rev. Clin. Lab. Sci. **2:** 103, 1971.
2. Skude, G.: Sources of the serum isoamylases and their normal range of variation with age, Scand. J. Gastroenterol. **10:** 577, 1975.
3. Green, C.: Identification of alpha-amylase as a secretion of the human Fallopian tube and "tube-like" epithelium of Müllerian and mesonephric duct origin, AM. J. OBSTET. GYNECOL. **73:** 402, 1957.
4. Hobbs, J. R., and Aw, S. E.: Urinary isoamylases, *in* Duback, U. C., editor: Enzymes in urine and kidney, Bern, 1968, Hans Huber, p. 281.
5. Vacikova, A.: Assessment of electrophoretic mobilities of some human isoamylases, J. Chromatogr. **69:** 349, 1972.
6. McGeachin, R. L., Hargan, L. A., Porter, B. A., and Daus, A. T.: Amylase in Fallopian tubes, Proc. Soc. Exp. Biol. Med. **99:** 130, 1958.
7. Skude, G., and Mårdh, P.-A.: Isoamylases in blood, urine, and tissue homogenates from some experimental animals, Scand. J. Gastroenterol. 1976. In press.
8. Mårdh, P.-A., Weström, L., von Mecklenburg, C., and Hammar, E.: Studies on ciliated epithelia of the human genital tract. I. Swelling of the cilia of Fallopian tube epithelium in organ cultures infected with *Mycoplasma hominis,* Br. J. Vener. Dis. **52:** 52, 1976.
9. Skude, G.: Electrophoretic separation, detection, and variation of amylase isoenzymes, Scand. J. Clin. Lab. Invest. **35:** 41, 1975.
10. Weström, L., Skude, G., and Mårdh, P.-A.: Amylases of the genital tract. II. Peritoneal fluid isoamylases in acute salpingitis, AM. J. OBSTET. GYNECOL. **126:** 657, 1976.

Amylases of the genital tract

II. Peritoneal fluid isoamylases in acute salpingitis

L. WESTRÖM, M.D.
G. SKUDE, M.D.
P.-A. MÅRDH, M.D.
Lund and Malmö, Sweden

The activities of the specific genital isoamylases in peritoneal fluid were diminished or absent in acute salpingitis. The decrease was proportional to the severity of the tubal inflammatory reactions but could not be related to a closure of the abdominal tubal ostia. In women with infections of the lower genital tract in whom the Fallopian tubes were normal at laparoscopy, the peritoneal fluid isoamylase activities were as high as in healthy women. Determination of the activities of specific genital isoamylases in peritoneal fluid obtained by cul-de-sac puncture would seem to constitute a specific diagnostic method for acute salpingitis. (AM. J. OBSTET. GYNECOL. 126: 657, 1976.)

LAPAROSCOPY OFFERS a valuable method for diagnosis of acute salpingitis.[1] However, routine use of laparoscopy requires facilities not generally available. Laboratory methods as diagnostic aids in patients with suspected infections of the Fallopian tubes so far have been of restricted value.

The epithelium of the Fallopian tubes produces isoamylases, which can be distinguished from pancreatic and salivary isoamylases in homogenates of Fallopian tube and in peritoneal fluid obtained from the cul-de-sac.[2, 3]

This study deals with isoamylases in the serum and peritoneal fluid of women with laparoscopically verified acute salpingitis, with infections confined to the lower genital tract, and in uninfected nonpregnant women.

From the Department of Obstetrics and Gynecology, University Hospital, Lund, the Department of Clinical Chemistry, University of Lund, Malmö General Hospital, Malmö, and, the Institute of Medical Microbiology, University of Lund, Lund.

Supported by grants from the Swedish Medical Research Council (Projects Nos. B76-13X-581-12B and B76-16X-04509).

Received for publication February 4, 1976.

Accepted May 19, 1976.

Reprint requests: Dr. L. Weström, Department of Obstetrics and Gynecology, University Hospital, S-221 85 Lund, Sweden.

Clinical material

Patients. Forty women with laparoscopically verified acute salpingitis and 15 women with infections confined to the lower genital tract.

Reference group. Fifteen nonpregnant women, age matched with the patients and having no signs of infection of either the lower or upper genital tracts, had laparoscopy as part of an investigation of involuntary childlessness or because of lower abdominal pain. In all the 15 nonpregnant control subjects, laparoscopy revealed normal conditions.

Methods

The clinical diagnosis of acute salpingitis was confirmed by laparoscopy, which was performed within 24 hours of the patient's admission to the clinic and before treatment was instituted. The laparoscopic technique used was similar to that described by Fear.[4] Salpingitis seen at laparoscopy was graded as mild, moderate, or severe, as earlier defined.[5]

The patients who were considered as having an infection confined to the lower genital tract fulfilled the following criteria: a history of a yellowish or malodorous vaginal discharge, a wet smear of the vaginal contents dominated by leukocytes, and normal Fallopian tubes at laparoscopy.

At laparoscopy, the small amount of peritoneal fluid present in the cul-de-sac was aspirated by means of a cannula inserted through a separate incision in the ab-

Table I. Mean values of the isoamylase activities (units per liter) in sera from the patients with acute salpingitis and infections of the lower genital tract and from the women of the reference group

	Acute salpingitis				
Isoamylases	*Mild*	*Moderate*	*Severe*	*LGTI**	*Reference group*
Pancreatic	67	75	93	83	90
Salivary	76	59	55	61	70
Total	143	134	148	144	160

*Lower genital tract infection.

Table II. Mean values of the isoamylase activities (units per liter) in peritoneal fluid from the patients with acute salpingitis and infections of the lower genital tract and from the women of the reference group. The quotient of the nonpancreatic isoamylase activities between peritoneal fluid and serum (P/S quotient) is given

	Acute salpingitis				
Isoamylase	*Mild*	*Moderate*	*Severe*	*LGTI**	*Reference group*
Pancreatic	45	48	52	46	40
Nonpancreatic	140	40	77	283	306
Total	185	88	129	329	345
P/S quotient†	1.96	0.77	1.27	4.88	4.82

*Lower genital tract infection.

†The lower limit for normal was regarded as 1.5.

dominal wall. This fluid and a serum sample obtained at the same time were used for amylase determinations.

Specimens for isolation of *N. gonorrhoeae* were collected from the urethral orifice, the cervix, and the rectum in all patients.

The amylase activity of serum and peritoneal fluid was determined as described in Part I of this study.[3]

Results

Serum isoamylases. The mean values of the *total amylase activity* in the sera of the patients with mild, moderate, and severe acute salpingitis ranged from 134 to 148 U. per liter; they did not differ from the corresponding values of the women with lower genital tract infection or from those of the women in the reference group (Table I). The mean values of the activities of the serum *salivary* and *pancreatic isoamylases* did not differ significantly between the groups of women investigated. The specific isoamylases of the genital tract were not detectable in serum.

Peritoneal fluid isoamylases. The mean *total amylase activity* in peritoneal fluid collected from the cul-de-sac in the patient with acute salpingitis ranged between 88 and 185 U. per liter and was significantly lower ($p < 0.05$) than the corresponding activity in the control group (345 U. per liter) and the patients with lower genital tract infection (329 U. per liter) (Table II).

The mean values of the *pancreatic isoamylase* activity in the peritoneal fluid specimens from the patients with acute salpingitis did not differ significantly from the corresponding mean values of the other two groups of women studied (Table II).

Our technique was incapable of distinguishing all the isoamylase fractions of genital origin from those of the salivary glands. Therefore, the sums of the activities of these two groups of isoamylases, i.e., *nonpancreatic isoamylases*, were determined in the peritoneal fluid specimens. In the patients with acute salpingitis, the mean values of these isoamylases ranged between 40 and 140 U. per liter. These mean values were significantly lower ($p < 0.05$) than the corresponding values in the patients with lower genital tract infections and the control subjects, in whom the values were 283 and 306 U. per liter, respectively (Table II). In the patients with acute salpingitis and laparoscopically mild inflammatory changes of the Fallopian tubes, the mean of the nonpancreatic isoamylase activities was 140 U. per liter. In the patients with moderately severe acute salpingitis, the corresponding mean activity was 40 U. per liter, and, in those with severe infection, the value was 77 U. per liter. In one woman with severe acute salpingitis, a value of 296 U. per liter was noted. In this woman, only one of the uterine tubes was infected—the other appeared normal. If this woman is excluded, the mean of the nonpancreatic isoamylase activities in the patients with severe acute salpingitis was 41 U. per liter.

The visual estimation of the contribution of the *specific genital* isoamylases to the peritoneal fluid, based on the staining intensity on the anodal side of the salivary mean fraction, revealed differences between the patients with acute salpingitis and those women in whom laparoscopy showed normal Fallopian tubes (Fig. 1). Of the 40 women with acute salpingitis, 30 had no detectable specific isoamylase activity in the peritoneal fluid (Table III), whereas in the group with lower genital tract infection all but three women and in the reference group all but one woman showed a marked contribution of these enzymes. A weak contribution of the specific genital isoamylases to the peritoneal fluid was seen in six of the 40 salpingitis patients, three of the 15 women with lower genital tract infection, and one of the 15 control subjects (Table III). Three women

with laparoscopically mild acute salpingitis and the woman with severe but one-sided acute salpingitis had a specific genital isoamylase contribution comparable to that of the control subjects.

The activities of the various isoamylases in the peritoneal fluid samples of the patients with acute salpingitis in whom *N. gonorrhoeae* was isolated from the lower genital tract did not differ from those of the patients who had negative cultures for gonococci, and no differences were observed between the patients with acute salpingitis of different ages.

Quotient of nonpancreatic isoamylase activities between peritoneal fluid and serum. Calculation of this quotient revealed significant differences between the patients with acute salpingitis and the women of the other two groups ($p < 0.05$; Table II). Thirty-four of the 40 patients with acute salpingitis had quotients less than 1.5, i. e., the lower limit for what was considered the normal quotient.

Comment

The activities of the specific isoamylases of the Fallopian tube epithelium, demonstrable in peritoneal fluid of healthy, nonpregnant women of childbearing age, were diminished or absent in acute inflammatory disorders of the tubal epithelium. The decrease was proportional to the severity of the inflammatory reactions of the tubes as seen at laparoscopy; the more severe the inflammatory reactions, the greater was the decrease in amylase activity. The decrease affected only the activities of the specific genital isoamylases, the pancreatic main fraction showing the same activity in peritoneal fluid of women with and without pelvic inflammatory disease. The amylase activities in fluid of the cul-de-sac of patients from whom gonococci were and were not isolated from the lower genital tract did not differ. In the patients with acute salpingitis, the decline in amylase activity in the peritoneal fluid did not seem to be the result of closure of the abdominal tubal ostia, as specific amylase activities were absent or weak in such fluid from the patients with acute salpingitis in whom the abdominal tubal ostia were still patent. The diminished activities of the specific isoenzymes in peritoneal fluid of patients with tubal infection might have been due to reduced production and/or release of the isoamylases from the inflamed tubal epithelium. Blocking of the activities of secreted enzymes might also have affected the possibility to detect them. However, any such reason for abolished activity of the specific genital isoamylases in peritoneal fluid was contradicted by the fact that the activities of these enzymes in peritoneal fluid of healthy women were not affected by the addition of peritoneal fluid obtained from women with acute salpingitis which lacked any such activity.

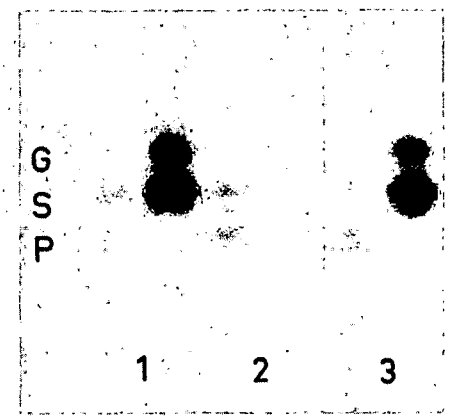


Fig. 1. Typical isoamylase patterns of serum and peritoneal fluid. In each sample pair, the serum pattern is to the left and the peritoneal fluid pattern is to the right. The anode is above. Sample pair 1: Normal nonpregnant women. Sample 2: Acute salpingitis. Sample 3: Infection of the lower genital tract. *P* = Pancreatic main isoamylase fraction; S = salivary main isoamylase fraction; G = genital tract–specific isoamylases.

Table III. Number of women with specific genital isoamylases in the peritoneal fluid as visually estimated from the staining intensity on the anodal side of the salivary main fraction

Genital amylase activity	*Acute salpingitis*			*LGTI**	*Reference group*
	Mild	*Moderate*	*Severe*		
None	7	18	5	0	0
Weak	3	2	1	3	1
Marked	3	0	1	12	14
Total	13	20	7	15	15

*Lower genital tract infection.

The amount of fluid in the cul-de-sac varied. However, there was no correlation between the amount of fluid and its isoamylase activities in any group of women investigated. This was true also when the quotients of *pancreatic* isoamylase activities between peritoneal fluid and serum were calculated.

Determinations of the electrophoretic isoamylase patterns in peritoneal fluid and serum revealed, in the present investigation, an abnormal peritoneal fluid/serum nonpancreatic amylase activity quotient in 85 per cent of the patients with acute salpingitis.

It is generally agreed that most tubal infections are caused by an infection ascending from the lower genital tract. In the group of patients judged as having an infection confined to the lower genital tract, the activities of the specific genital isoamylases in peritoneal fluid were normal in 12, weak in two, and completely

abolished in one. The latter three might have had endosalpingitis, not detectable at laparoscopy. Those three patients were treated with antibiotics, for which reason the further course of possible incipient endosalpingitis could not be evaluated.

For an experienced laparoscopist, the diagnosis of even slight inflammatory reactions of the uterine tubes is seldom difficult. In the present investigation, there was a good correlation between the laparoscopic findings and the results of the amylase determinations. All patients who had signs of bilateral inflammatory reactions of the Fallopian tubes (except three with very slight tubal changes) showed a significant reduction of amylase activity in the fluid aspirated from the cul-de-sac. The physiologic changes in the Fallopian tubes, seen at menstruation, for instance, may be misinterpreted by a less experienced laparoscopist as a sign of tubal infection. In such cases, and in patients with endosalpingitis not detectable at laparoscopy, determination of the activities of the specific genital isoamylases in peritoneal fluid might be of dignostic value.

The diminished activities of the specific genital isoamylases in the peritoneal fluid observed in pregnant women[3] may be caused by a mechanism other than infections of the tubes, because a one-sided tubal infection did not influence the isoamylase activities, whereas an intrauterine pregnancy did.

In most women, there is no difficulty in obtaining peritoneal fluid by puncture of the cul-de-sac via the posterior vaginal fornix. In a continuation of this study, such punctures were performed immediately before laparoscopy in 16 patients. The procedure was successful in 13 of these cases. No complications occurred. Determination of the specific genital isoamylases in peritoneal fluid obtained by this technique seems to offer a safe, simple, and specific means for the diagnosis of acute salpingitis.

REFERENCES

1. Jacobson, L., and Weström, L.: Objectivized diagnosis of acute pelvic inflammatory disease, Am. J. Obstet. Gynecol. **105:** 1088, 1969.
2. Green, C.: Identification of alpha-amylase as a secretion of the human Fallopian tube and "tube-like" epithelium of Müllerian and mesonephric duct origin, Am. J. Obstet. Gynecol. **73:** 402, 1957.
3. Skude, G., Mårdh, P.-A., and Weström, L.: Amylase of the genital tract. I. Isoamylase in genital tract tissue homogenates and peritoneal fluid. Am. J. Obstet. Gynecol. **126:** 652, 1976.
4. Fear, R. E.: Laparoscopy: A valuable aid in gynecologic diagnosis, Obstet. Gynecol. **31:** 297, 1968.
5. Weström, L.: Effect of acute pelvic inflammatory disease on fertility, Am. J. Obstet. Gynecol. **121:** 707, 1975.

Immunologic studies in patients with trophoblastic neoplasia

YUTAKA TOMODA, M.D.
MASAKAZU FUMA, M.D.
NORIHIKO SAIKI, M.D.
NAOTAKA ISHIZUKA, M.D.
TATSUYA AKAZA
Nagoya, Japan

Histocompatibility antigen was analyzed in 1,104 patients with trophoblastic neoplasia and in their husbands. Furthermore, the patients were examined for cell-mediated immunity. (1) There was no significant difference in the frequency of the ABO blood groups between patients with hydatidiform or destructive mole or choriocarcinoma and healthy persons. (2) The incidence of appearance of anti-HL-A antibody was more frequent in the patients with destructive mole than in those with hydatidiform mole or choriocarcinoma. (3) Patients with choriocarcinoma were frequently incompatible at HL-A9, HL-A10, and HL-AW5. (4) The mixed lymphocyte culture (MLC) showed lower values in patients with choriocarcinoma than in those with destructive mole. Histocompatibility between the patients and their husbands was more remarkable in the patients with chriocarcinoma than in those with destructive mole. (5) In patients with choriocarcinoma, incompatibility was detected at HL-A10, HL-A11, HL-AW5, and HL-A13 in the group with good prognosis and at HL-A5, HL-AW15, and HL-A12 in the poor prognosis group. The MLC value was lower in the poor prognosis group.
(AM. J. OBSTET. GYNECOL. 126: 661, 1976.)

TROPHOBLASTIC NEOPLASIA arising from trophoblastic cells having received paternal and maternal histocompatibility genes can be regarded as an allogeneic graft. Although part of it might be rejected, the remainder grows.

To study the pathogenesis of this tumor, it seemed useful to investigate the histocompatibility of trophoblastic cells and host, and the immunologic response of the host to histocompatibility antigens.

This report describes histocompatibility in patients with trophoblastic neoplasia and in their husbands and the capacity of patients for cell-mediated immunity.

From the Department of Obstetrics and Gynecology, School of Medicine, Nagoya University, and the Department of Clinical Laboratory, Aichi Cancer Center Hospital.

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare.

Received for publication November 24, 1975.

Accepted March 3, 1976.

Reprint requests: Dr. Y. Tomoda, Dept. of Obstetrics and Gynecology, Nagoya University School of Medicine, Tsurumai-Cho, Showa-Ku, Nagoya, Japan.

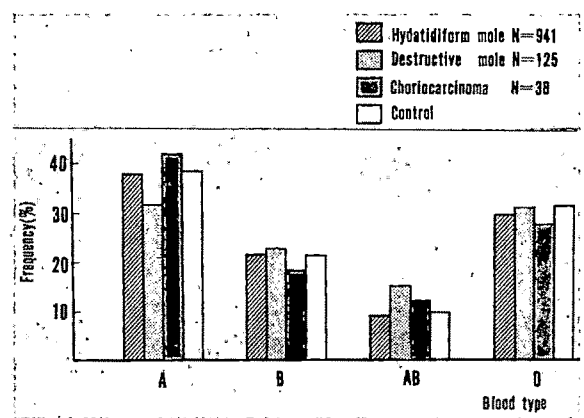


Fig. 1. Frequency of ABO blood groups in the patients with trophoblastic neoplasia.

Materials and methods

The subjects studied were both inpatients and outpatients with trophoblastic neoplasia treated in the Department of Gynecology and Obstetrics, School of Medicine, Nagoya University. They were histologically diagnosed and categorized based on the choriocarcinoma risk score described by Ishizuka.[1] The patients

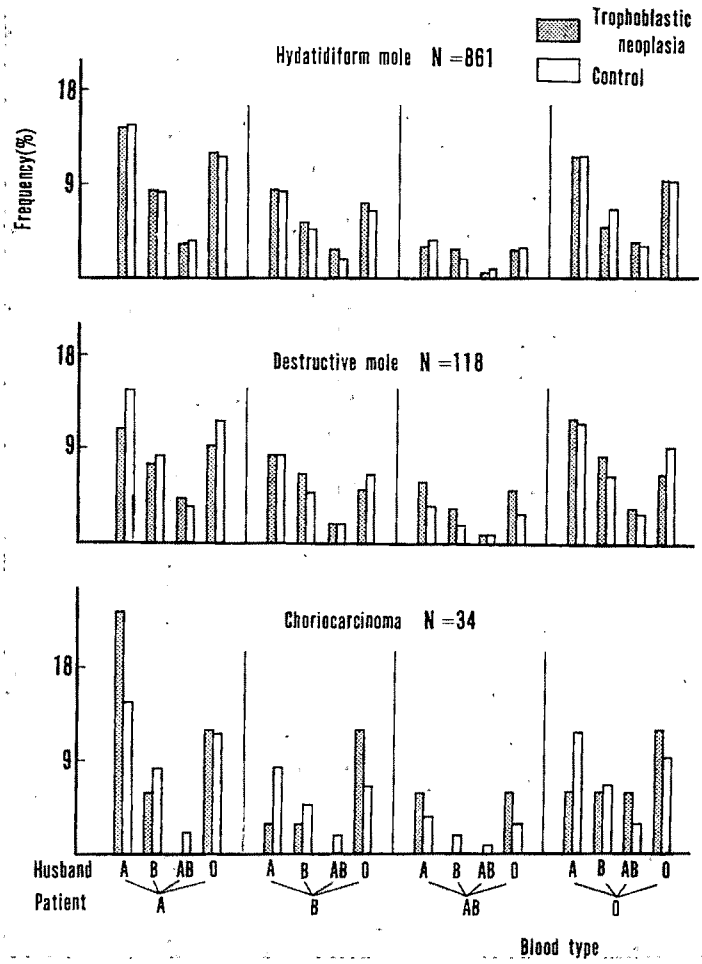


Fig. 2. Frequency of ABO blood groups in the patients with trophoblastic neoplasia and their husbands.

were divided into the following three groups: (1) 941 patients with hydatidiform mole, (2) 125 patients with destructive mole, and (3) 38 patients with choriocarcinoma.

The ABO blood groups were determined with routine methods and HL-A types with the microlymphocyte toxicity method described by Amos.[2] The 54 anti–HL-A sera used were supplied by the United States National Institute of Health. Mixed lymphocyte culture (MLC)[3] was used in the test of histocompatibility in patients and their husbands. The cell-mediated immunity of the host was examined by the phytohemagglutinin-induced lymphocyte transformation (PHA-T). Anti–HL-A antibodies were detected with the microlymphocyte toxicity method using lymphocytes collected from 48 healthy subjects. The antibody titer was determined in 18 specimens.

Results

ABO blood groups. Fig. 1 shows the frequency of the ABO blood groups in patients with hydatidiform mole, destructive mole, and choriocarcinoma. There was no difference in blood type frequency between the patients with hydatidiform mole and healthy Japanese individuals. There was a tendency for type AB to be slightly predominant in patients with destructive mole, but no statistical significance ($0.1 > p > 0.05$). Of the patients with choriocarcinoma, 42.1 per cent belonged to type A, 18.4 per cent to type B, 13.2 per cent to type AB, and 26.3 per cent to type O. Fig. 2 shows the frequency of the ABO blood groups in the patients and their husbands. There was no difference in the frequency of blood type among patients with hydatidiform mole and the average Japanese person.

In patients with choriocarcinoma, the cases where both patients and their husbands belonged to type A seemed to be somewhat predominant, but the difference was not statistically significant.

The compatibility of trophoblastic neoplasia with the host was investigated. Fig. 3 shows the compatibility of the blood types of the hosts with those of the child which could be presumed from the blood types of

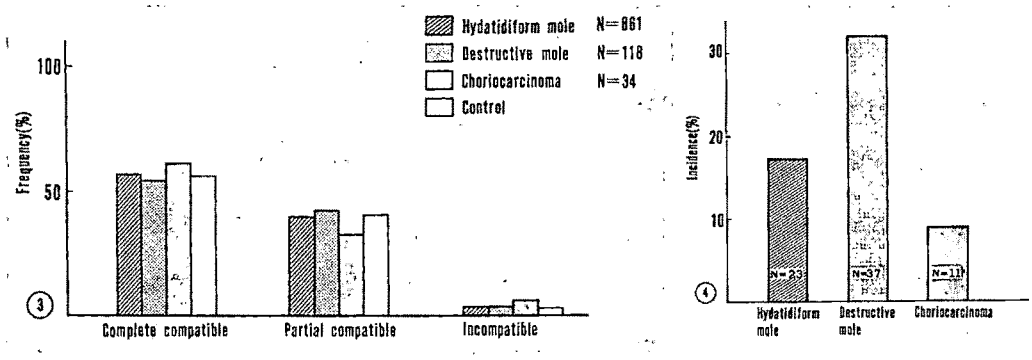


Fig. 3. Compatibility of ABO blood groups between the patients with trophoblastic neoplasia and their children. ABO blood groups in children were presumed by types of patients and their husbands.

Fig. 4. Incidence of anti–HL-A antibodies in the patients with trophoblastic neoplasia.

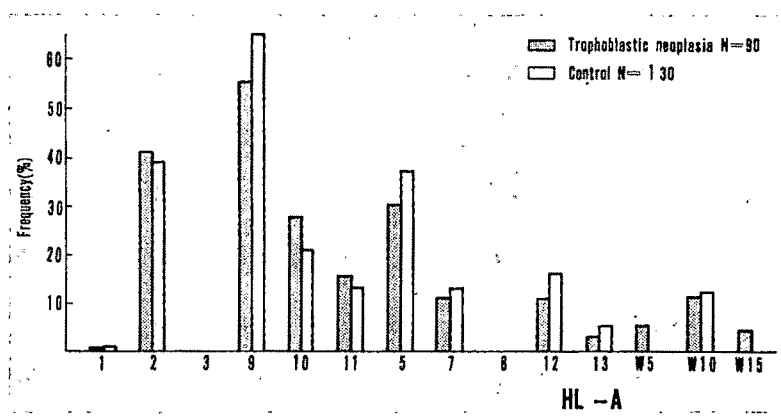


Fig. 5. Frequency of HL-A in the patients with trophoblastic neoplasia.

the patients and their husbands. There was no significant difference between the results obtained and the theoretical value calculated from the average value of the Japanese population as a whole. Thus, no distinct relationship was found between the occurrence of trophoblastic neoplasia and the ABO blood groups.

Anti–HL-A antibodies. Anti–HL-A antibodies in serum were examined in 71 patients with trophoblastic neoplasia, excluding those who had previously received a blood transfusion. A high incidence was found in patients with destructive mole. These antibodies were also detected in patients with hydatidiform mole and chriocarcinoma (Fig. 4). A high titer of monospecific anti–HL-A antibody was found in three cases. Anti–HL-A antibodies were detected in two patients who had suffered hydatidiform mole in their first pregnancy. These data suggest the presence of histocompatibility antigens in the cells of trophoblastic neoplasia.

HL-A typing. There was no significant difference in the frequency of HL-A among patients with trophoblastic neoplasia (N = 90) and healthy Japanese subjects (N = 130) (Fig. 5). The frequency of HL-A in patients is shown in Fig. 6. HL-A11 and HL-A12 were seen in patients with destructive mole a little less frequently than in healthy subjects. In patients with choriocarcinoma, HL-A10 and HL-A11 were more frequent and HL-A5 was less. There was no difference in frequency between patients with hydatidiform mole and the control group. Fig. 7 indicates the results of studies on the compatibility between patients with trophoblastic neoplasia and their husbands. In patients with neoplasia, the incompatibility was the most remarkable around one (Fig. 7). Incompatibility with HL-A9, HL-A10, and HL-AW5 was more frequent in patients with choriocarcinoma than in those with other types of neoplasia (Fig. 8).

Mixed lymphocyte culture (MLC). The value of MLC (two-way) was examined to study the histocompatibility among patients with trophoblastic neoplasia and their husbands. The MLC value was much lower ($P < 0.02$) in patients with choriocarcinoma than in those with hydatidiform or destructive mole (Fig. 9).

Histocompatibility antigen in choriocarcinoma. Cases of choriocarcinoma can be divided into two groups on the basis of their clinical course. One is a

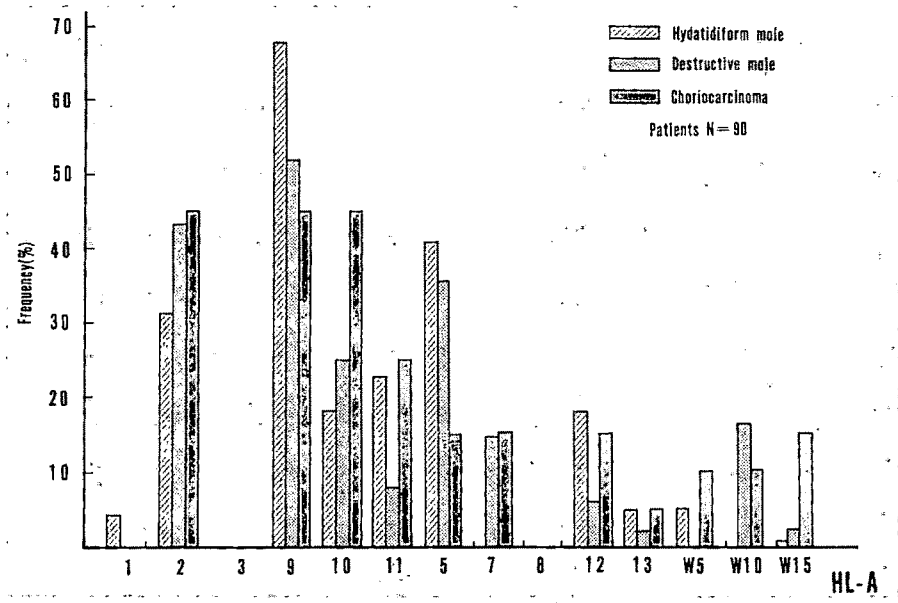


Fig. 6. Frequency of HL-A in the patients with hydatidiform mole, destructive mole, and choriocarcinoma.

group with good prognosis; these patients have a remission after treatment. The other is a group with poor prognosis; these patients show no response to treatment. The cases in the present study were also divided into two groups. Incompatibility of HL-A of the husbands and their wives (patients) was analyzed. Incompatibility was found in HL-A10, 11, W5, and 13 in the group with a good prognosis, and in HL-A5, W15, and 12 in the group with a poor prognosis. Incompatibility was detected in HL-A9, W10, 2, and 7 in both groups (Tables I and II). The MLC value was lower in the poor prognosis group than in the good prognosis group. There was, thus, a difference in HL-A incompatibility between the two groups. These findings suggest that histocompatibility antigen influences the prognosis of choriocarcinoma.

Cell-mediated immunity. The phytohemagglutinin-induced lymphocyte transformation (PHA-T) was examined in patients with trophoblastic neoplasia. The value was lower ($p < 0.05$) in patients with choriocarcinoma than in those with destructive mole and in healthy women (Fig. 10), suggesting that cell-mediated immunity might have been reduced in patients with choriocarcinoma.

Sera from patients with trophoblastic neoplasia were examined for effect on PHA-T of normal lymphocytes (Fig. 11). The effect of serum at the stage of remission was used as control (regarded as 100 per cent) in the patients with choriocarcinoma and destructive mole. The effect of serum at the time when the hCG level decreased to the normal pituitary LH level served as control in the patients with hydatidiform mole. The effect of serum on PHA-T was compared between patients before treatment and those during treatment. PHA-T was suppressed by sera from patients with choriocarcinoma and destructive mole before and during treatment, whereas it was stimulated by sera from four out of five patients with hydatidiform mole before treatment. An immune suppressive factor might be present in sera from patients with choriocarcinoma and destructive mole.

Comment

Scott[4] reported that blood types A and AB were predominant in 46 patients with trophoblastic neoplasia. Llewellyn-Jones[5] stated that types B and O were decreased and type AB increased in 140 patients with neoplasia. Dawood, Teoh, and Ratnam[6] reported that type A was predominant while type B was less frequent, and that type AB was frequently found in patients with choriocarcinoma and a poor prognosis. Bagshawe and co-workers[7] stated that patients of type A, particularly those who had husbands with type O, were predominant, and that the prognosis was poor in patients of type AB with choriocarcinoma. In the present investigation, 1,104 patients were classified as to ABO type. We found no abnormality in the frequency of blood types, except that a combination of the patient with type A and a husband of type A was slightly more frequent in the case of choriocarcinoma. Blood types (ABO system) in Japanese patients are not related to the development or prognosis of trophoblastic neoplasia.

Currie,[8] Van Rood and co-workers,[9] and Lawler,

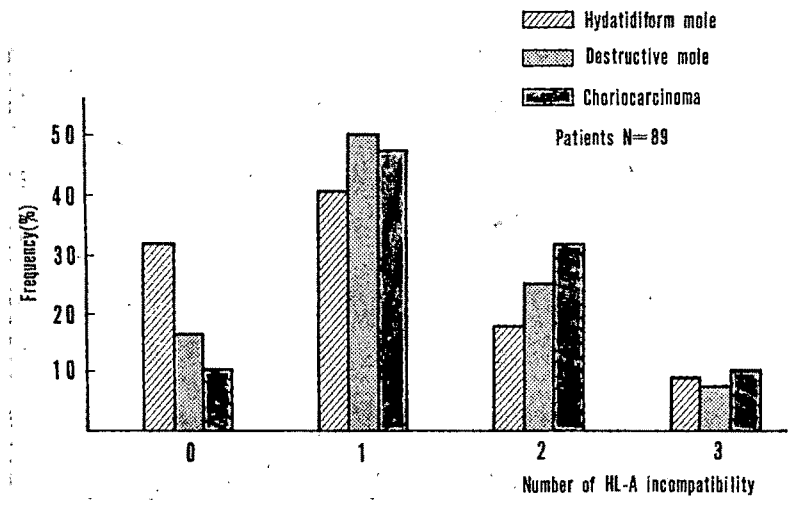


Fig. 7. Incompatibility of HL-A between the patients with trophoblastic neoplasia and their husbands.

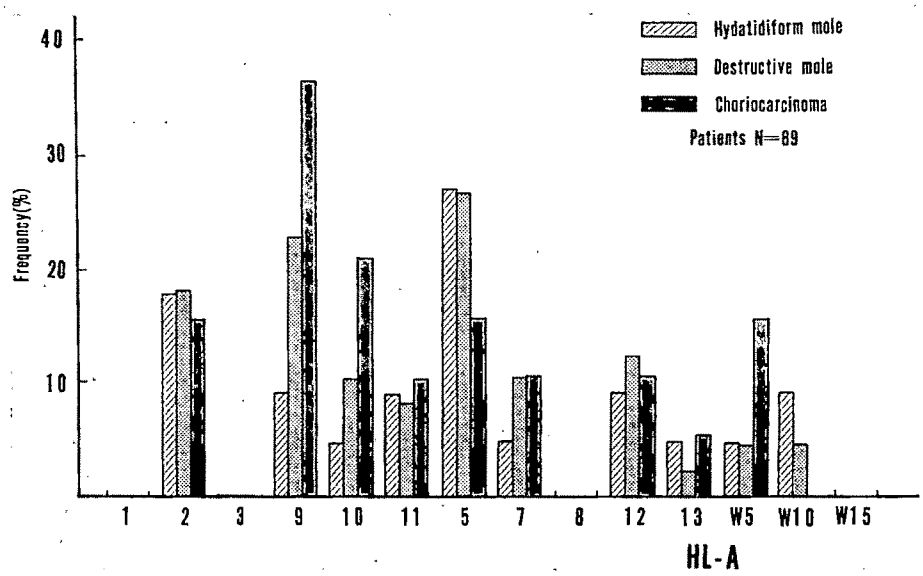


Fig. 8. Incompatibility of HL-A between the patients with hydatidiform mole, destructive mole, and choriocarcinoma and their husbands.

Klowda, and Bagshawe[10] reported that trophoblastic cells contained histocompatibility antigens. We demonstrated anti-HL-A antibody in two women in whom the first pregnancy had resulted in hydatidiform mole, suggesting that trophoblastic cells contain HL-A. Appearance of anti-HL-A antibody was less frequent in patients with choriocarcinoma than in those with destructive mole. It was suggested that the antigenicity of HL-A is so weak in the case of choriocarcinoma that neoplasia is not readily rejected.

Recently, attention has been paid to the relationship between histocompatibility antigen and certain diseases. Lilly, Boyse, and Old[11] studied the relationship between H-2 and leukemia in mice. Feltkamp, Van den Berg-Loonen, and Nuen huis[12] pointed out in myasthenia that HL-A2 and HL-A8 were related to the time of onset and the form of clinical manifestation. No such studies, have been performed on trophoblastic neoplasia. In the present study, there was no difference in the frequency of HL-A between the patients with trophoblastic neoplasia as a whole and the control. However, the frequency of appearance of HL-A showed a slight difference between patients with choriocarcinoma and destructive mole and the control.

It seems important for an understanding of the pathogenesis of trophoblastic neoplasia to elucidate whether histocompatibility antigen of this tumor is compatible with the host or not. Mogensen and Kissmeyer-Nielsen[13] carried out HL-A typing in 12 patients with choriocarcinoma and their families. They

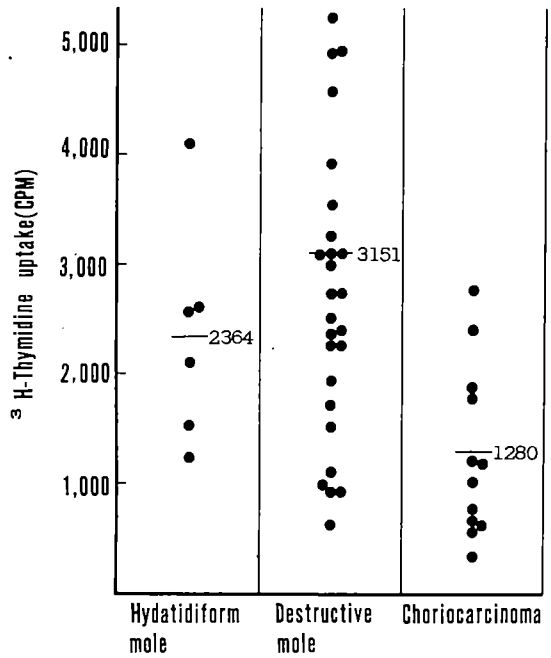


Fig. 9. The reactivity of mixed lymphocyte culture (MLC) in the patients with trophoblastic neoplasia and their husbands.

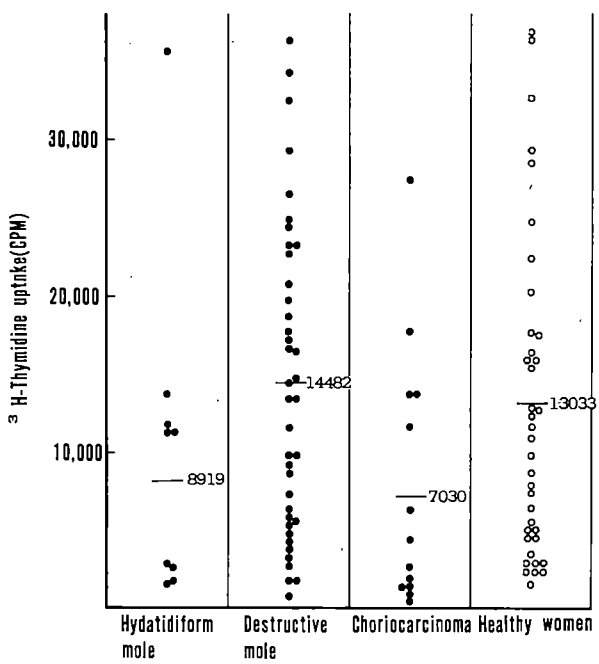


Fig. 10. Phtohemagglutinin-induced lymphocyte transformation (PHA-T) in the patients with trophoblastic neoplasia.

reported that histocompatibility antigen of a child was compatible with his mother (patient) in 11 familes out of 12 and suggested that there might be a compatibility of histocompatibility antigen between neoplasia and patient.

We examined the number of cases in which there was incompatibility of HL-A between patients and their

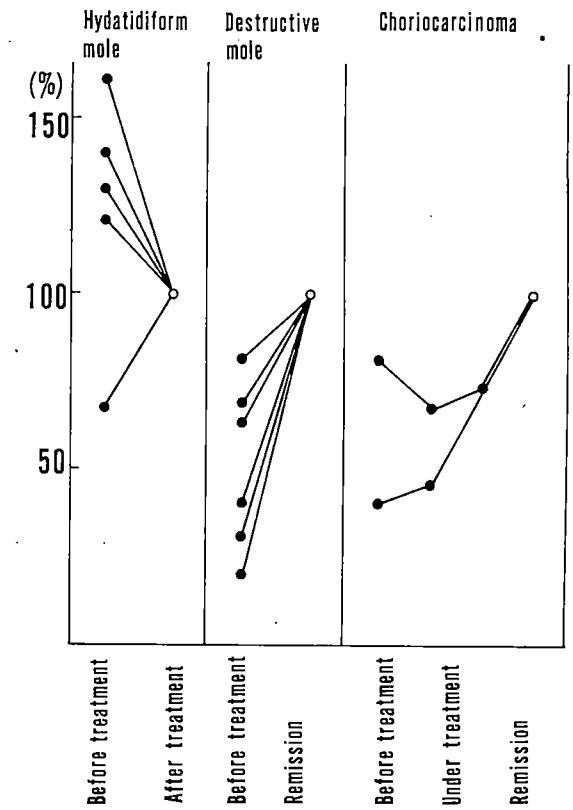


Fig. 11. Effect of sera from the patients with trophoblastic neoplasia on phytohemagglutinin-induced lymphocyte transformation (PHA-T) in normal woman.

husbands. There was no difference in any types of trophoblastic neoplasia. The frequency of appearance of such incompatibility was analyzed by the type of HL-A. It was a little high in HL-A9, HL-A10, and HL-AW5 in the case of choriocarcinoma. The patients with choriocarcinoma were divided into two groups on the basis of prognosis after treatment. No histopathologic difference was observed. There was a difference, however, in the pattern of incompatibility of HL-A between the good and poor prognosis groups. Besides, the MLC value was lower in the poor than in the good prognosis group. These results suggest that there is a difference in antigenicity of histocompatibility antigen in the cases of choriocarcinoma and that it might be possible to distinguish two group; that is, one group exhibiting strong antigenicity against the host and the other group exhibiting weak antigenicity against the host.

Takeuchi and Kanazawa[14] reported that the value of PHA-T was significantly lower in the case of choriocarcinoma than in the case of hydatidiform or destructive mole. Similar results were obtained in the present study. It has been pointed out that sera from patients with malignant neoplasia contain a factor suppressing immunity. No such factor has been reported in patients

Table I. Histoincompatibility between the patients with choriocarcinoma with good prognosis and their husbands

Pt.	*Duration of treatment (mo.)*	*HL-A*			*MLC (c.p.m.)*	*ABO (P/H)*
		Patient	*Husband*	*Incompatibility*		
Y. Y	2	10/W10	9, 11/7, W10	9, **11**,* 7	2,890	O/A
M. I	5	9, 10	2, 9	2	6,571	A/A
K. K	2	2, 10	2/W5	**W5**	—	A/A
T. I	2	9/7	10/W5, W10	**10, W5,** W10	4,217	O/B
T. H	5	2, 9/5	9/5	(—)	1,792	AB/A
S. H	12	2, 9/7	11/13	**11,13**	5,281	B/B
H. O	6	2	2	(—)	1,021	O/AB
K. O	4	2/12	2, 9	9	1,229	A/O
A. M	4	2, 9	9, 10/7, W5	**10,** 7, **W5**	2,761	B/O
Y. S	5	9, 11/W5	2, 10	2, **10**	—	A/O
K. T	6	10	10	(—)	1,829	A/A
M. A	3	10/5	9/5	9	657	A/A
Average value					2,825	

*Boldface indicates HL-A incompatibility with good prognosis.

Table II. Histoincompatibility between the patients with choriocarcinoma with poor prognosis and their husbands

Pt.	*Prognosis*	*HL-A*			*MLC (c.p.m.)*	*ABO (P/H)*
		Patient	*Husband*	*Incompatibility*		
K. A	Died	10, 11/12, W15	9, 10/7, W10	9, 7, W10	—	AB/A
H. K	Died	2, 11/W10	9, 11/5, W15	9, **5, W15**	2,771	A/A
I. K	Died	10/12, W5	2	2	2,387	A/A
Y. S	Died	2, 11	9	9	1,228	A/O
Y. S	Died	2/12, 13	9/5, 12	9, **5**	334	A/B
K. M	Died	9/5, 12	9/5	(—)	2,236	A/B
R. O†		9, 10/5, W15	9/12, W10	**12,** W10	786	A/O
Y. Y‡		9, 10/7	—	—	—	A/
H. O§		9, 11	9/5	**5**	593	B/A
Average value					1,476	

*Boldface indicates HL-A incompatibility with poor prognosis.
†Under treatment for 7 years.
‡Under treatment for 2 years.
§Under treatment for 1 years.

with trophoblastic neoplasia. The present investigation revealed that PHA-T is reduced in the patients with choriocarcinoma, and that the serum shows an action to suppress PHA-T in patients with choriocarcinoma and destructive mole. On the other hand, the serum stimulated PHA-T in the patients with hydatidiform mole. Therefore, it was presumed that in the patients with hydatidiform mole, cell-mediated immunity was not so suppressed that neoplasia might be rejected. It may be interpreted that in patients with choriocarcinoma, the neoplasia grow readily in the hosts, since cell-mediated immunity is reduced and there may be higher compatibility between neoplasia and host.

REFERENCES

1. Ishizuka, N.: J. Jap. Obstet. Gynecol. Soc. **21:** 1443, 1969.
2. Amos, D. B.: Manual of tissue typing technique, NIH, p. 1, 1970.
3. Kuramochi, T.: Jap. J. Transplant. **6:** 88, 1971.
4. Scott, J. S.: Am. J. Obstet. Gynecol. **83:** 185, 1962.
5. Llewellyn-Jones, D.: J. Obstet. Gynaecol. Br. Commonw. **72:** 242, 1965.
6. Dawood, M. Y., Teoh, E. S., and Ratnam, S. S.: J. Obstet. Gynaecol. Br. Commonw. **78:** 918, 1971.
7. Bagshawe, K. D., Rawlins, G., Pike, M. C., and Lawler, S. D.: Lancet **1:** 553, 1971.
8. Currie, G. A.: J. Obstet. Gynaecol. Br. Commonw. **74:** 841, 1967.
9. Van Rood, J. J., Van Leeuwen, A., Schippers, A., and Balner, H.: Cancer Res. **28:** 1415, 1968.
10. Lawler, S. D., Klowda, P. T., and Bagshawe, K. D.: Am. J. Obstet. Gynecol. **120:** 857, 1974.
11. Lilly, F., Boyse, E. A., and Old, L. J.: Lancet 2: 1207, 1964.
12. Feltkamp, T. E. W., Van den Berg-Loonen, P. M., and Nuen huis, L. E.: Br. Med. J. **1:** 131, 1974.
13. Mogensen, B., and Kissmeyer-Nielsen, F.: Lancet **1:** 721, 1968.
14. Takeuchi, S., and Kanazawa, K.: Acta Obstet. Gynecol. Jap. **19:** 59, 1972.

Fertility in women with gonadal dysgenesis

F. I. REYES, M.D.
K. S. KOH, M.D., B.S.
C. FAIMAN, M.D., M.Sc.
Winnipeg, Manitoba, Canada

A successful pregnancy in a patient with a 45,X/47,XXX karyotype who had premature menopause is described. Review of the literature revealed an additional 24 cases of fertility in women with gonadal dysgenesis associated with a 45,X chromosomal line. Their reproductive history showed a total of 58 pregnancies. However, abortion, stillbirth, and abnormal progeny, including five with chromosomal errors, were common. Therefore, such patients should be advised regarding their reduced fertility potential and the possibility of abnormal offspring. (AM. J. OBSTET. GYNECOL. 126: 668, 1976.)

PRIMARY AMENORRHEA is one of the characteristic features of the syndrome of gonadal dysgenesis. However, patients with this condition, including individuals with a 45,X chromosome constitution, may menstruate and even be fertile.[1] The first report of fertility in gonadal dysgenesis appeared in 1960,[2] and since then only isolated case reports have followed.

In this communication we report a case of successful pregnancy in a patient with a 45,X/47,XXX karyotype and review the reproductive history of similar cases in the literature.

Case report

Mrs. D. C., a 33-year-old woman, gravida 1, para 1, was referred to our Reproductive Endocrine Clinic because of secondary amenorrhea of 18 months' duration. Menarche was at the age of 10 years and was followed by regular menstrual cycles. She conceived at 21 years of age. The pregnancy and delivery were normal. The puerperium was uneventful, and she received lactation-suppression treatment. Afterwards her menses returned, but the cycle intervals were of one to three months in duration, and she did not again become pregnant. From age 24 to 26 years, she used oral contraception and had normal withdrawal bleeding. After discontinuation of the oral contraceptive medication, oligomenorrhea and involuntary infertility persisted. At the age of 31 years, menses ceased, and she began to have mild sporadic hot flushes and night sweats. Physical examination revealed the following features of the gonadal dysgenesis syndrome: short stature (142 cm.), high arched palate, low nuchal hairline, short fourth metacarpals, and multiple pigmented nevi. Other features, such as webbing of the neck, cubitus valgus, hypertension, and lymphedema, were absent. Sexual hair was normal, and the breasts were well developed. The uterus was also normal, and the ovaries were not palpable.

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by radioimmunoassay (RIA) with the use of a human pituitary gonadotropin standard (LER-907). Both serum FSH (104 to 234 μg per deciliter) and LH (26.2 to 39.3 μg per deciliter) levels were elevated, and serum estradiol concentrations (by RIA) were low (<1.0 ng. per deciliter). These results are indicative of primary ovarian failure, i.e., a premature postmenopausal state. Skull and chest x-ray examinations disclosed no abnormalities. Short fourth metacarpals were confirmed radiologically.

A buccal smear preparation showed 25 per cent single and 10 per cent double X-chromatin bodies suggestive of mosaicism. Karyotype determination revealed two cell lines in both skin fibroblasts (49 cells examined) and lymphocytes (30 cells examined): 45,X/47,XXX. The proportion between X:XXX lines was 9:1 in the blood and 5:1 in the skin.

The phenotype of the patient's 12-year-old daughter was normal. She had normal stature and pubertal sexual characteristics, and no stigmas of gonadal dysgenesis. Chromosomal analysis showed a 46,XX karyotype with no abnormalities by conventional and banding techniques.

From the Departments of Obstetrics and Gynaecology, Physiology, and Medicine, University of Manitoba, and the Health Sciences Centre.

Received for publication March 23, 1976.
Revised June 10, 1976.
Accepted June 21, 1976.

Reprint requests: Dr. F. I. Reyes, (SO-21) Health Sciences Centre, 700 William Ave., Winnipeg, Manitoba, Canada R3E 0Z3.

Table I. Reproductive history of women with gonadal dysgenesis

Karyotype	*Patients (No.)*	*Pregnancies (No.)*	*Pregnancy outcome*				*Reference*
			Unknown	*Abortion*	*Stillbirth*	*Live birth*	
45,X	4	5	—	—	1	4	2-5
46,X/46,XX	9	26	1	11*	1**	13	6-13
45,X/47,XXX	4	6	—	—	—	6	14, 15, and present report
45,X/46,XX/46,XXX	8	21	—	8	2†	12‡	16-22
Total	25	58	1	19	4	35	

*Therapeutic abortion in one case.
†Malformed fetuses
‡One set of twins

Table II. Normality of progeny of women with gonadal dysgenesis

Offspring		*No.*	*Reference*
Not examined		8	11, 15, 16
Normal		15	2-5, 7, 8, 12, 13, 18, 21, and present report
Abnormal		12	6, 10, 11, 17-20, 22
Gonadal dysgenesis	5		
Down's syndrome	3		
Hydrocephaly	1		
Spina bifida	1		
Congenital heart disease	1		
Bowel malformation	1		
Total		35	

Table III. Chromosomal constitution in offspring with gonadal dysgenesis

Maternal karyotype	*Offspring karyotype*	*Reference*
45,X/46,XX	45,X/46,XX	12
45,X/46,XX/47,XXX	45,X/46,XX	17
	45,X/46,XX*	
	45,X/46,XX/47,XXX*	
45,X/46,XX/47,XXX	45,X/46,XX	20

*Twins.

Comment

Only 24 case reports of fertile women with gonadal dysgenesis were found in the literature (Table I). According to Ferguson-Smith,[1] only about 8 per cent of patients with a 45,X karyotype and 21 per cent with a 45,X/46,XX chromosomal constitution may have spontaneous menses. This difference explains the greater number of pregnancies in women with mosaicism. Moreover, it is also possible that the four fertile women with a 45,X karyotype[2–5] might, in fact, be cases of undetected mosaicism with a normal ovarian 46,XX line.[23] Nevertheless, germ cells may survive to adulthood in some instances, since Carr and associates[24] have found that not all ovaries from 45,X infants are abnormal. Usually, the normal oocyte population of 45,X embryos undergoes rapid atresia and germ cells are absent at birth.

When the short and irregular menstrual histories of women with gonadal dysgenesis is considered,[1, 25, 26] the total of 58 pregnancies achieved by the 25 patients is remarkable (Table I). The oldest age at conception on record is 31 years.[2] However, there were 19 abortions, one of which was therapeutic, four stillbirths, three of them with multiple malformations, and 35 live births, including one set of twins (Table I). Furthermore, as shown in Table II, of the total of 35 live births, twelve children were definitely abnormal, eight had chromosomal aberrations (Table III), and four had gross neural, cardiac, or intestinal malformation. Five of them died at an early age. There are insufficient or no data at all regarding eight offspring. It is worth noting that one died in early childhood with leukemia.[21] Thus, of a total of 58 pregnancies in 25 women, only 15 can be considered successful with certainty.

These findings suggest that abortion and abnormal progeny are common in these women. Nevertheless, it is not possible to establish the true frequency of these events, since a number of the mothers were examined retrospectively. In addition, biases of reporting could exist.

The elevated frequency of gonadal dysgenesis in the offspring (Tables II and III) suggests that the maternal abnormal chromosome constitution may lead to nondysjunction in the fertilized ovum. A comparable observation has been described in 47,XXX individuals.[27] The cases of neural, cardiac, and intestinal malformations are difficult to explain; however, they are most probably unrelated to maternal aneuploidy. The high number of abortions, stillbirths, and mongolism could be associated with premature ovarian aging, since these

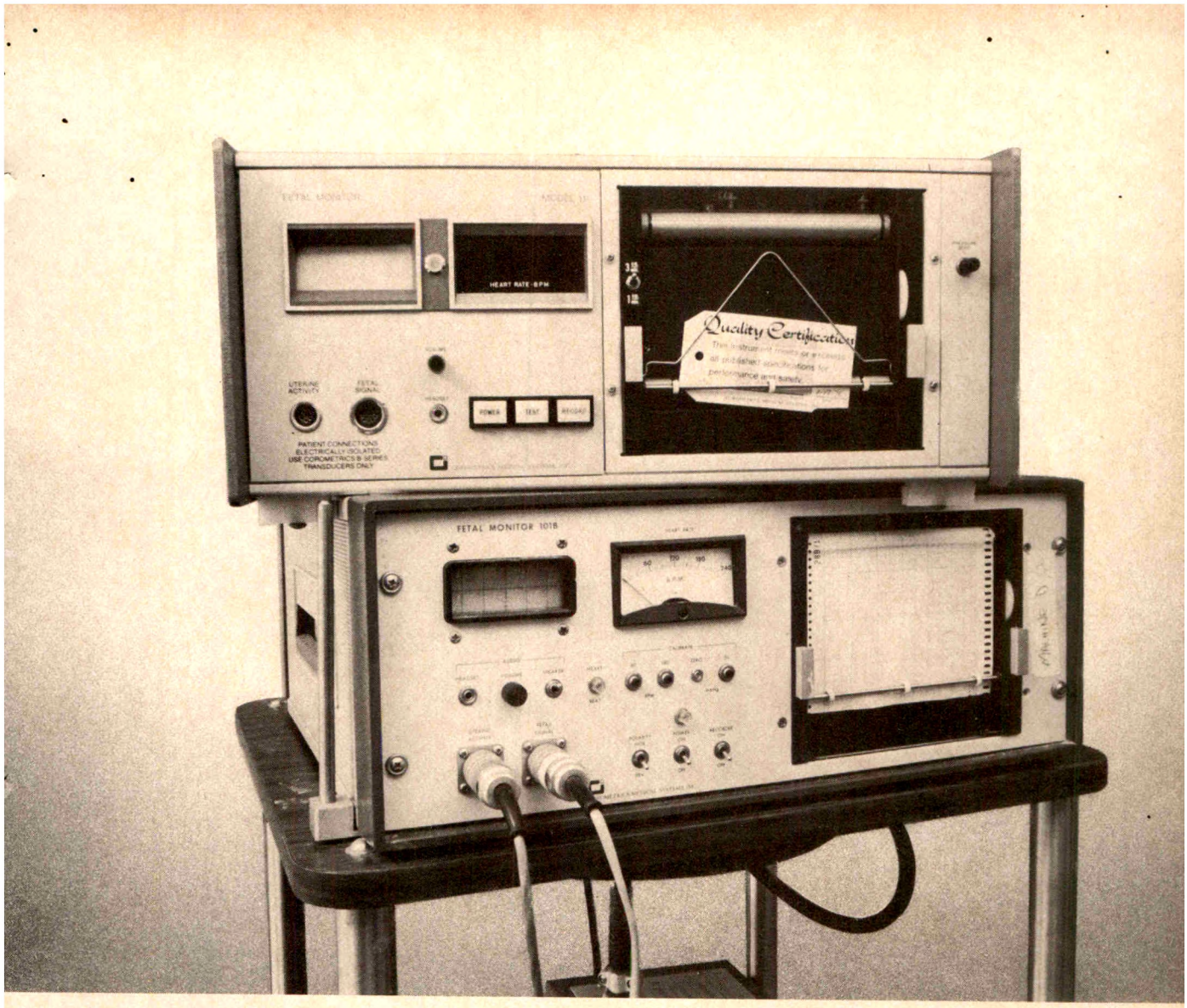
abnormalities also occurr frequently in normal premenopausal women.[28]

Young patients with gonadal dysgenesis who exhibit spontaneous menses should be made aware that in their condition: (1) fertility is reduced, (2) the reproductive life period is shorter, and (3) the possibilities of abortion and abnormal offspring are perhaps higher than normal. Moreover, in view of the high risk of offspring having a chromosome abnormality with malformations, amniotic fluid studies should be carried out early in pregnancy to rule out these possibilities.

We thank Dr. T. M. Baskett for his referral of the patient and wish to acknowledge our appreciation to Professor J. L. Hamerton, Director of the Genetics Department, Health Sciences Centre, for the genetic studies and his helpful suggestions.

REFERENCES

1. Ferguson-Smith, M. A.: Fertility in a 45X/46XX patient, J. Med. Genet. **2:** 142, 1965.
2. Bahner, E., Schwarz, G., Hienz, H. A., and Waeter, K.: Turner-syndrom mit voll ausgebildeten sekundären Geschlechtsmerkmalen und Fertilität, Acta Endocrinol. **35:** 397, 1960.
3. Nakashima, I., and Robinson, A.: Fertility in a 45,X female, Pediatrics **47:** 770, 1971.
4. Grace, J. H., Quinlan, D. K., and Edge, W. E. B.: 45,X Lymphocyte karyotype in a fertile woman, AM. J. OBSTET. GYNECOL. **115:** 279, 1973.
5. Groll, M., and Cooper, M.: Menstrual function in Turner's syndrome, Obstet. Gynecol. **47:** 225, 1976.
6. Bishun, N. P., Rashad, M. N., Morton, W. R. M., Mannion, P. L., Neely, M. R., and Burke, G.: Chromosomal mosaicism in a case of repeated abortion, Lancet **1:** 936, 1969.
7. Bomers-Marres, A. J. M. L.: Een fertiele vrouw met een X0 (45)/XX(46)-mozaïek, Ned. Tijdschtr. Geneeskd. **110:** 1177, 1966.
8. MacKay, E. V., Cockburn, K. G., and Biggs, J. G. S.: Clinical and chromosomal study of 4 patients with XX/XO mosaicism, Aust. N. Z. J. Obstet. Gynaecol. **7:** 64, 1967.
9. Kava, H. W., and Klinger, H. P.: Secondary infertility in a phenotypically normal 45,X/46,XX female, Fertil. Steril. **19:** 835, 1968.
10. Predescu, V., Christodorescu, D., Tăutu, C., Ciovîrnache, M., and Constantinescu, E.: Repeated abortions in a woman with XO/XX mosaicism, Lancet **2:** 217, 1969.
11. Arakaki, D. T., and Waxman, S. H.: Cytogenetics of spontaneous abortion, AM. J. OBSTET. GYNECOL. **107:** 1199, 1970.
12. Siegelman, M.: XO/XX and XO/XY mosaicism, Obstet. Gynecol. **39:** 510, 1972.
13. Lieber, E., and Berger, J.: Fertility in a 45X/46XX patient, Lancet **1:** 199, 1973.
14. Lewis, F. J. W., Poulding, R. H., and Eastham, R. D.: Acute leukaemia in an XO/XXX mosaic, Lancet **2:** 306, 1963.
15. Maclean, N., Court-Brown, W. M., Jacobs, P. A., Mantle, D. J., and Strong, J. A.: A survey of sex chromatin abnormalities in mental hospitals, J. Med. Genet. **5:** 165, 1968.
16. Briggs, D. K., Stimson, D. W., and Vinogrod, J.: Leukocyte anomaly, mental retardation and dwarfism in a family with abnormal chromosomes, J. Pediatr. **63:** 21, 1963.
17. DeToni, E., Massimo, L., Vianello, M. J., and Podesta, F.: La casistica di un anno di attivita del centro di Studi Cromosomici della Clinica Pediatrica di Genova nel campo delle malformazione sessuali, Minerva Pediatr. **17:** 578, 1965.
18. Armendares, S., Buentello, L., Sánchez, J., and Ortiz, M.: Mosaicism without Turner's stigmata, Lancet **2:** 820, 1967.
19. Nielsen, J., and Thomsen, N.: A psychiatric-cytogenetic study of a female patient with 45/46/47 chromosomes and sex chromosomes XO/XX/XXX, Acta Psychiatr. Scand. **44:** 141, 1968.
20. Giraud, F., Hartung, M., Brusquet, Y., Mattei, J. F., Sebahoun, A., Serment, H., Stahl, A., and Bernard, R.: La fertilite des femmes 45,X/46,XX et 45,X/46,XXX/47,XXX, Ann. Genet. **13:** 255, 1970.
21. Hsu, L. Y. F., Palo-García, F., Grossman, D., Kutinsky, E., and Hirschorn, K.: Fetal wastage and maternal mosaicism, Obstet. Gynecol. **40:** 98, 1972.
22. Kim, J. H., Hsu, L. Y. F., Paciuk, S., Cristian, S., Quintana, A., and Hirschorn, K.: Cytogenetics of fetal-wastage, N. Engl. J. Med. **293,** 844, 1975.
23. Rimoin, D. L., and Schimke, R. N.: Genetic Disorders of the Endocrine Glands, St. Louis, 1971, The C. V. Mosby Company, p. 290.
24. Carr, D. H., Haggar, R. C., and Hart, A. G.: Germ cells in the ovaries of XO female infants, Am. J. Clin. Pathol. **49:** 521, 1968.
25. Kaufman, S.: Vaginal bleeding in gonadal dysgenesis, Pediatrics **37:** 26, 1966.
26. McDonough, P. G., Byrd, J. R., and Freedman, M. A.: Gonadal dysgenesis with ovarian function, Obstet. Gynecol. **37:** 868, 1971.
27. Bergemann, E.: Manifestation familiale du karyotype triplo-X, J. Genet. Hum. **10:** 370, 1962.
28. Talbert, B.: Effect of maternal age on reproductive capacity, AM. J. OBSTET. GYNECOL. **10:** 451, 1968.



NUMBER ONE IS STILL HARD AT WORK

Corometrics® 101 Fetal Monitor (serial number 101118001) has undergone some changes since its 1969 installation in New York Metropolitan Hospital. And it isn't tired yet.

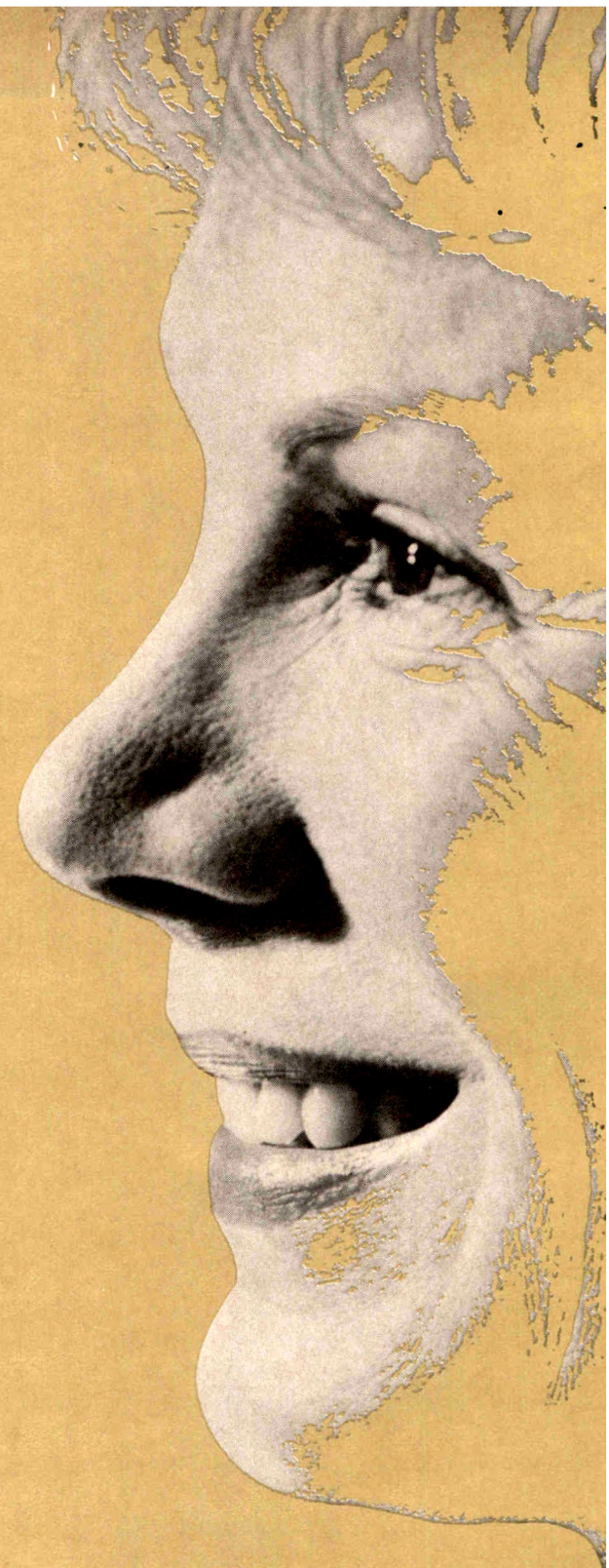
In 1971, it was modified to 101A monitor specifications, providing more flexibility. Then, in 1973, the front panel and other internal changes made it a 101B, capable of both direct and indirect monitoring.

That same quality, integrity and reliability that went into the 101 Fetal Monitor seven years ago are found in the 111 Fetal Monitor today. Our Service Department can update your instrument to provide you with the latest state-of-the-art modifications. Our national network of Sales Consultants and Service Engineers are available to help you with your individual requirements. For expansion of present equipment, our Systems Department can provide you with many options engineered to individual specifications. And for education in the practical applications of monitoring, Corometrics RN Perinatal Specialists periodically conduct community workshops throughout the year.

It's all part of our Total Product Support. Our customers are Number One. And we're working hard to keep it this way.

COROMETRICS MEDICAL SYSTEMS, INC.
Barnes Industrial Park
Wallingford, Connecticut U.S.A. 06492
Telephone: [203]265-5631 Telex: 940 403

Estrogen replacement therapy moves forward



the major human estrogen micronized for oral effectiveness

Estrace®
(estradiol)

1-mg. and 2-mg. scored tablets

- not esterified, not conjugated
- estradiol...the active estrogen at the cellular level

from Mead Johnson

overall, 95% of patients studied gained adequate or complete relief of their symptoms[1]

Estrace (estradiol) was given to 369 estrogen-deficient women for periods ranging up to a year or more (average of six months); 319 of these women received an initial dosage of 1 or 2 mg. per day and were evaluated for efficacy. *Complete disappearance* of hot flushes was experienced by 227 (76%) of 298 women, of sweating by 131 (80%) of 164 women, of tingling by 62 (94%) of 66 women, and of genital atrophy by 44 (88%) of 50 women. In general, 95% of the patients evaluated experienced either adequate or complete relief of their symptoms. Remarkably, in 77% of the patients, symptoms were controlled without need to adjust the initial dosage—usually 2 mg. daily. (Dosage after adjustment ranged from 1 mg. to 3 or 4 mg. a day.)[1]

cyclic therapy recommended

Recently, published reports of retrospective human data have emphasized that patients using estrogens may have an associated increased risk of endometrial cancer. This information makes cyclic rather than continuous estrogen replacement therapy even more prudent. (See brief summary.)

With Estrace, treatment should be initiated with a dose of 1 or 2 mg. daily and then adjusted to the lowest dose possible still maintaining the relief of symptoms. The usual regimen for cyclic administration of Estrace is three weeks on drug, followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4–6 days) to prevent recurrence of menopausal symptoms.

estradiol...orally effective

The technique of micronization has opened up the oral route to natural human estrogen replacement with Estrace. Reduced particle size of the estradiol in Estrace makes effective gastrointestinal absorption possible. Onset of action is rapid, with marked increases in levels of circulating estradiol and estrone; concomitant decreases in serum concentrations of FSH and LH are sustained over a 24-hour period.[2]

Because estradiol can be assayed in plasma, Estrace can provide objective[2] as well as clinical evidence[1] of ready availability and biologic activity.

well accepted by patients[1]

In the 369 patients previously described, the incidence of estrogen-induced side effects with Estrace was relatively low. Incidence of nausea was remarkably low—only 2% of patients before dosage adjustment. Some patients who had complained of this problem while on conjugated equine estrogens reported its complete disappearance on changing to Estrace. Whereas before dosage adjustment 24% experienced breast tenderness, 31% edema, 18% (of 151 with intact uteri) bleeding, and 4% weight gain, only about 2% of the 369 patients dropped out because of side effects.[1]

long-term therapy should be monitored

A few instances of significant gynecologic disease became apparent during clinical investigations.[1] Endometrial hyperplasia was discovered in seven patients, all of whom had previously received estrogen therapy for one to three years prior to entering the study. One patient was reported to have carcinoma *in situ* and another showed adenocarcinoma of the endometrium. In clinical practice, the physician should be alerted to the potential of thrombotic disorders and be prepared to discontinue medication immediately if they occur. Because of variations in normal endogenous hormone production, certain patients may exhibit signs of excessive estrogenic stimulation. Adverse reactions generally associated with estrogen administration may occur and these are listed in the brief summary. Prior to initiation of treatment with Estrace or any other estrogenic preparation, an adequate physical examination should be given.

References

1. Callantine, M.R., *et al.*: Micronized 17β-estradiol for oral estrogen therapy in menopausal women, Obstet. Gynecol. *46*:37–41 (July) 1975.
2. Yen, S.S.C., *et al.*: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β-estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. *40*:518–521 (March) 1975.

For Brief Summary, please see following page.

Estrogen replacement therapy moves forward...

Estrace® (estradiol)

the major human estrogen micronized for oral effectiveness



Indications: Estrace® (17β-Estradiol) is indicated for relief of endogenous estrogen deficiency and associated menopausal symptoms.

Contraindications: Estrace® is contraindicated in patients with 1) markedly impaired liver function; 2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible; 3) known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium; 4) undiagnosed abnormal genital bleeding; 5) thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions; and 6) pregnancy.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen medication should be stopped. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

Adverse Reactions: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis). The following adverse reactions are known to occur in patients receiving estrogens: nausea, vomiting, anorexia, gastrointestinal symptoms (such as abdominal cramps or bloating), edema, breakthrough bleeding, spotting or withdrawal bleeding, breast tenderness and enlargement, change in body weight (increase or decrease), headache, increased cervical mucus, allergic rash, loss of libido and gynecomastia in the male, reactivation of endometriosis, aggravation of migraine headaches, hepatic cutaneous porphyria becoming manifest, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, cystitis-like syndrome, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, possible diminution in lactation when given immediately post-partum, irritability, and malaise.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than non-users to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study. In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients. Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued. It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase th risk of vaginal adenocarcinoma developing years later in the offspring exposed.

(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Childbearing Age, Brit. Med. J., 2:193-199, 1968. (3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969. (5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970. (6) Herbst, et al. — Adenocarcinoma of the Vagina — New England Journal of Medicine. Vol. 284, Number 16 (April 22, 1971).

Dosage and Administration: Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol. Dosage may be adjusted to control the presenting symptoms depending on the response of the individual patient; the minimal effective dose for maintenance therapy should be determined by titration. To avoid continuous stimulation of the reproductive tract and breasts, cyclic therapy is recommended. The usual regimen consists of three weeks on drug followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4-6 days) to prevent recurrence of menopausal symptoms. Withdrawal bleeding of unusual amount or duration should be investigated.

How Supplied: Estrace® 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace® 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Mead Johnson LABORATORIES

© 1976 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. MJL 5-4127

Urgent need for OBGYN men; Hospital and/or private practice; 3500 deliveries per year; Northwestern Pennsylvania location, situated on the shore of Lake Erie. Salary negotiable. Reply to: Robert G. Timmons, M.D., Director, Medical Education. Hamot Medical Center, P.O. Box 339, Erie, Pennsylvania 16512.

GYNECOLOGIC ENDOCRINOLOGIST

Applications are invited for a faculty position for a fully-trained and certified obstetrician-gynecologist with formal training or experience in reproductive endocrinology and/or infertility to join an active, aggressive and productive program. Send complete resume and letters of reference to: James R. Givens, M.D., Director, Div. of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee, Center for the Health Sciences, 800 Madison Avenue, Memphis, Tennessee 38163. An equal opportunity employer.

THE OFFICE OF CONTINUING EDUCATION
BAYLOR COLLEGE OF MEDICINE
Houston, Texas

announces
its

THIRD BIENNIAL POSTGRADUATE COURSE ON

DISEASES OF THE VULVA AND VAGINA
JANUARY 13-15, 1977

Presented by

Department of Obstetrics and Gynecology
Baylor College of Medicine

Program Directors: Dr. Herman L. Gardner,
Clinical Professor
Department of Obstetrics and Gynecology

Dr. Raymond H. Kaufman,
Professor and Ernst W. Bertner Chairman,
Department of Obstetrics and Gynecology
and Professor, Department of Pathology

Twenty internationally known physicians including Baylor faculty will conduct a three-day course covering viral infections of the vulva and vagina; the common vulvo vaginitidies; vulvar dystrophies; dermatoses, fungal infections, venereal diseases; and carcinoma in situ and invasive carcinoma. The purpose of the course is to offer registrants a detailed update review of diseases involving these areas.

CONTINUING EDUCATION CREDIT HOURS WILL BE AVAILABLE.

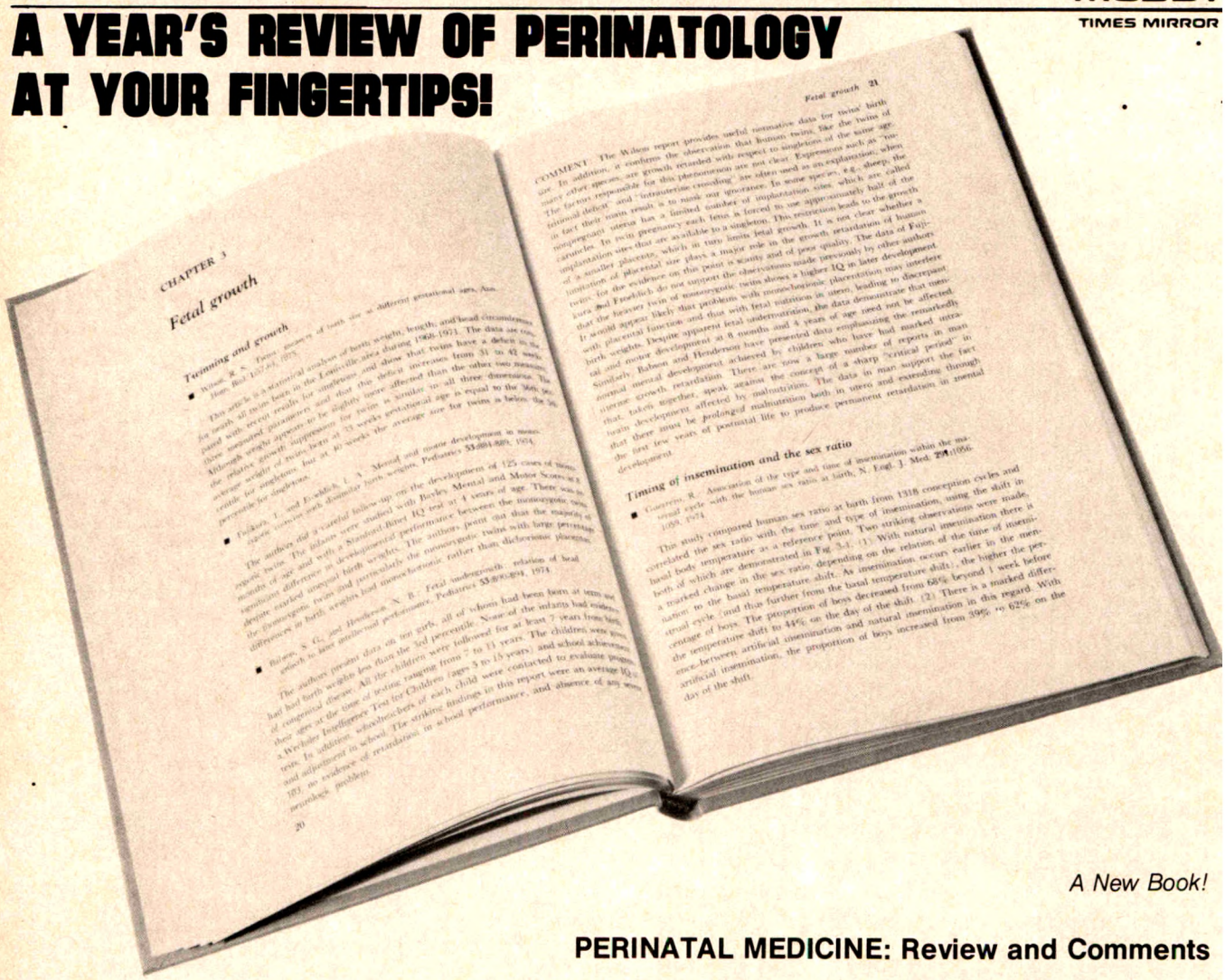
**MARK YOUR CALENDAR NOW—
JANUARY 13-15, 1977**

(Program to be published by November)

For further information contact:
Office of Continuing Education
Baylor College of Medicine
Texas Medical Center
Houston, Texas 77030
(713) 790-4941

MOSBY
TIMES MIRROR

A YEAR'S REVIEW OF PERINATOLOGY AT YOUR FINGERTIPS!



A New Book!

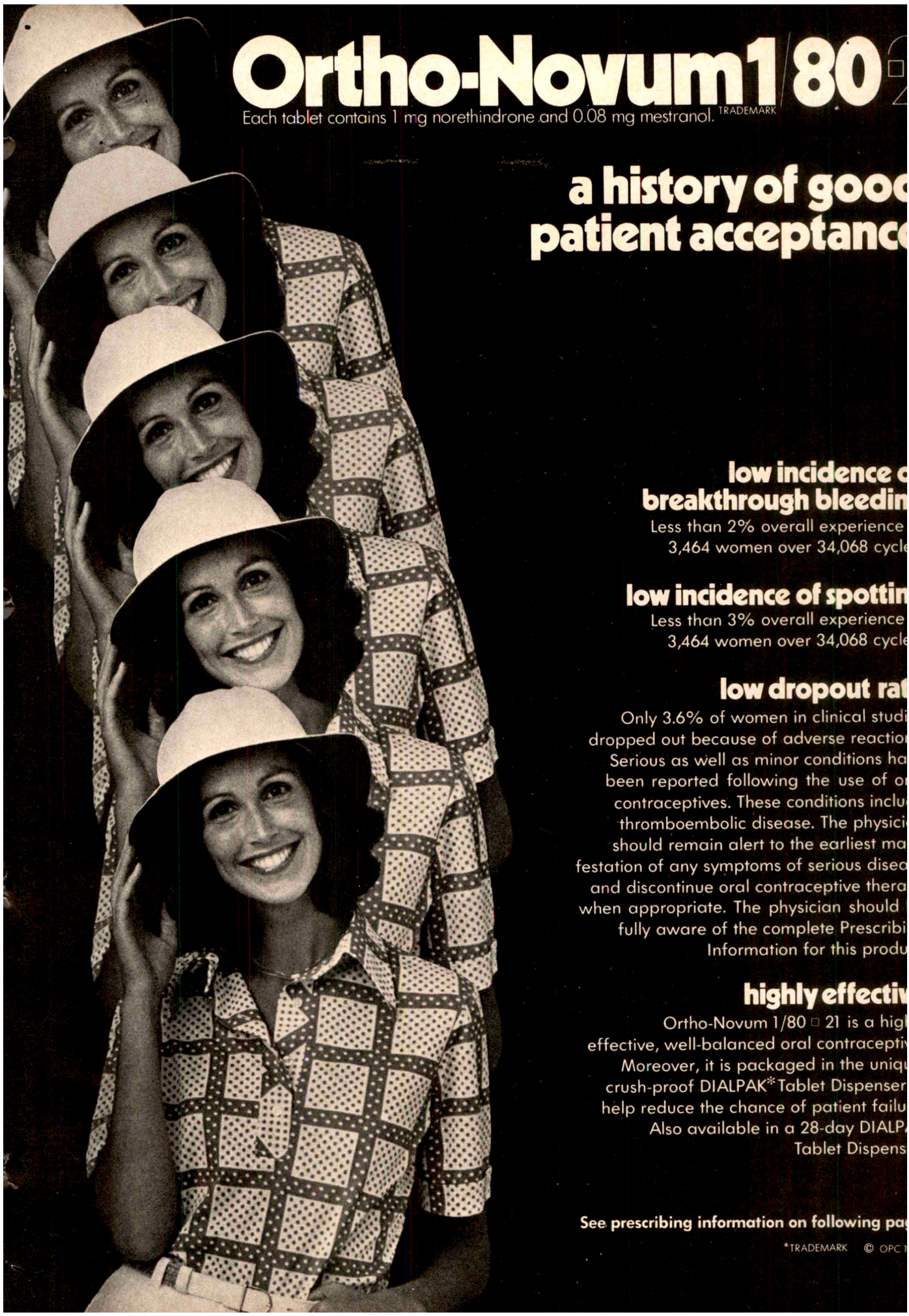
PERINATAL MEDICINE: Review and Comments

Now you can have a review of significant international literature on perinatology right at your fingertips! The first in a series of important volumes, this book presents summaries and comments on significant articles which have appeared during the year 1974. The authors have carefully selected these exceptionally informative articles from a wide variety of sources to provide you with information on more than 15 different subject areas of perinatal medicine. The three authors (a pediatrician, a physiologist, and an obstetrician) use their valuable knowledge and experience to relate the findings of these articles to other studies and to practical clinical problems you might encounter in your practice. The most recent developments are discussed in light of earlier studies — giving you a total view of this growing field. Among the many fascinating topics examined are: fetal metabolism, nutrition, fetal oxygenation, placental growth, fetal monitoring, birth injuries, respiratory problems of the newborn, infection, water and electrolyte balance, and much more! Rely on this series of volumes to keep you informed of the latest advances in perinatology!

Edited by Frederick C. Battaglia, M.D.; Giacomo Meschia, M.D.; and E. J. Quilligan, M.D. July, 1976. 146 pages plus FM I-XII, 6¾″ × 9¾″, 32 illustrations. Price, $18.50.

ORDER BY PHONE!
Call (800) 325-4177 ext. 10. In Missouri call collect — (314) 872-8370 ext. 10. 9 am to 5 pm (CST), Monday through Friday.

MOSBY
TIMES MIRROR
THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141



Ortho-Novum 1/80 □ 2

Each tablet contains 1 mg norethindrone and 0.08 mg mestranol. TRADEMARK

a history of good patient acceptance

low incidence of breakthrough bleeding

Less than 2% overall experience
3,464 women over 34,068 cycle

low incidence of spotting

Less than 3% overall experience
3,464 women over 34,068 cycle

low dropout rat

Only 3.6% of women in clinical studi
dropped out because of adverse reaction
Serious as well as minor conditions ha
been reported following the use of or
contraceptives. These conditions inclu
thromboembolic disease. The physici
should remain alert to the earliest ma
festation of any symptoms of serious disea
and discontinue oral contraceptive thera
when appropriate. The physician should
fully aware of the complete Prescribi
Information for this produ

highly effectiv

Ortho-Novum 1/80 □ 21 is a high
effective, well-balanced oral contraceptiv
Moreover, it is packaged in the uniqu
crush-proof DIALPAK* Tablet Dispenser
help reduce the chance of patient failu
Also available in a 28-day DIALP
Tablet Dispens

See prescribing information on following pag

*TRADEMARK © OPC

Ortho-Novum 1/80 ▫21 and 28

TRADEMARK

Each white tablet contains 1 mg norethindrone and 0.08 mg mestranol.
Each green tablet in the 28-day regimen contains inert ingredients.

a history of good patient acceptance



Ortho-Novum 1/80□21 and Ortho-Novum 1/80□28

Description: Each white ORTHO-NOVUM 1/80 tablet contains 1 mg of the progestational substance, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol. Each green tablet in the 28-day regimen contains inert ingredients.

Actions: ORTHO-NOVUM 1/80▫21 and ORTHO-NOVUM 1/80▫28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/80▫21 and ORTHO-NOVUM 1/80▫28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28. Therefore, if such tests are abnormal in a patient taking ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 may mask the onset of the climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during ORTHO-NOVUM 1/80▫21 or ORTHO-NOVUM 1/80▫28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme. Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health, 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.I.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:241-245, May 3, 1975. **12.** Mann, J.I.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J. J.; Nora, A. H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291*(14):697-700, Oct. 3, 1974.

OJ 719-5 R

Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

OBSTETRICS

Maternal cardiovascular dynamics

VII. Intrapartum blood volume changes

KENT UELAND, M.D.

Seattle, Washington

Blood volume was measured in 75 normal pregnant women at term and serially at 10 and 60 minutes and on Days 1 and 3 post partum in women delivered vaginally and on Days 1, 3, and 5 in women who underwent cesarean section. The mean blood volume at term was 5.95 L. and 83.3 c.c. per kilogram, an increase of 44 and 16 per cent, respectively, over nonpregnant values. The increment appeared to be related to lean body mass and the weight of the neonate alone and to the combined weights of the neonate and placenta, but the wide range of values precluded statistical significance. The blood volume loss at 60 minutes post partum was 610 c.c. (10.2 per cent) for patients delivered vaginally and 1,030 c.c. (17.4 per cent) for those delivered by cesarean section. The blood volume showed a steady decline to Day 3 post partum in the vaginal delivery group, whereas it remained fairly stable from 60 minutes to Day 5 post partum in the surgically delivered group. Remarkably, the volume had declined by the same amount, 16.2 per cent, in both groups on the third postpartum day. On the other hand, the hematocrit showed a rise of 5.2 per cent in the former group and a decline of 5.8 per cent in the latter. A remarkable tolerance for blood loss at delivery was demonstrated. A more realistic definition of postpartum hemorrhage is strongly recommended. (AM. J. OBSTET. GYNECOL. 126: 671, 1976.)

MANY INVESTIGATORS have studied the maternal circulatory changes accompanying pregnancy. One of the major alterations is an increase in blood volume. Although there are discrepancies in the literature, in regard to both the total increment in blood volume and the pattern of change throughout pregnancy, there is general agreement that the rise is one of significant proportions. The percentage increase has been found to range between 20 and 100.[18] When expressed in terms of body weight, the blood volume near term ranges between 73 and 96 c.c. per kilogram.[2, 10, 14, 16, 20, 21] The extent of this variation is attributed in part to the different techniques employed in measuring blood volume. In addition, many factors known to affect maternal blood volume frequently were not considered, such as: the physical stature of the patient, the weight of the fetus or products of conception,[12] the maternal posture in which blood volume was determined,[8] whether or not iron was used prophylactically,[6] or whether or not salt restriction was imposed, with or without the use of diuretics.

It is becoming increasingly evident that our past estimates of blood loss surrounding parturition have been in error. Several investigators using different techniques recently have shown that the amount of

From the Department of Obstetrics and Gynecology, University of Washington School of Medicine.

Received for publication April 2, 1976.

Accepted April 12, 1976.

Reprint requests: Dr. Kent Ueland, Department of Obstetrics and Gynecology, University of Washington, RR602, RH-20, Seattle, Washington 98195.

blood lost at vaginal delivery approximates 500 to 600 c.c.[2, 9, 11, 18, 24] and that during cesarean section delivery this amount is more than doubled.[2, 11, 18, 22, 23, 25] However, discrepancies still exist, not so much regarding blood loss at delivery but rather pertaining to blood volume changes accompanying the first few days of the puerperium.

It is not the author's intent to review or analyze critically techniques for measuring plasma volume and red blood cell volume. Chesley's[7] recent excellent discussion of the topic suffices. Rather, this study was undertaken to delineate term pregnancy blood volume in a large group of normal women and to compare serially the changes in blood volume that occur with parturition and the early puerperium in women undergoing vaginal and cesarean section delivery.

Methods

The patient population consisted of normal pregnant women with a gravidity of one through five who received their prenatal care at Harborview Medical Center and University Hospital, Seattle, Washington. Prophylactic iron was prescribed prenatally, but no effort was made to determine whether or not it was taken regularly. Diuretics were not prescribed, and no patients were placed on a sodium-restricted diet. The determinations were made prior to the onset of labor or prior to cesarean section, at 10 minutes and one hour after delivery, and on postpartum Days 1 and 3 for vaginal deliveries and on Days 1, 3, and 5 in patients undergoing cesarean section. The indicator was 1 to 5 μCi of Rihsa* (I^{131}–human serum albumin). The blood volume was estimated by the Volemetron* (a semiautomatic blood volume computer). Prior to the determination of the initial blood volume, each patient received 20 drops of a saturated solution of iodine in order to prevent selective uptake of any free radioactive iodine by the maternal and fetal thyroid glands. A control sample of blood was withdrawn from a large antecubital vein. All blood sampling was accomplished without a tourniquet and with the patient in supine recumbency. The hematocrit, along with a base-line measurement of radioactivity, was determined from this sample in duplicate. A measured dose of I^{131}-tagged albumin was then injected into a vein of the opposite arm, and the syringe was carefully flushed with blood by fully withdrawing the plunger and reinjecting three times in order to assure that the entire dose was delivered to the patient intravenously. Residual radioactivity in the syringe and needle was then subtracted from the dose administered to the patient to give the net amount of substance injected. At precisely ten minutes, another sample of venous blood was withdrawn from an antecubital vein of the opposite arm. The carefully measured and thoroughly mixed samples of blood obtained before and after injection of I^{131}-tagged albumin were then placed in counting chambers, and the blood volume was automatically computed from the differences in their radioactivity. To assure reproducibility in results and consistency in technique, all determinations were meticulously performed by the investigator. Although the I^{131}-tagged albumin was dispersed in the plasma, a constant sampling site, careful sampling techniques, and thorough mixing of plasma and red cells before counting would ensure a constant distribution of the tagged substance in whole blood.

*Ames Atomium.

Principles underlying measurement of blood volume with the Volemetron apparatus. If one assumes uniform distribution of the test substance injected (I^{131}), then:

$$V \text{ (volume)} = \frac{N \text{ (amount of substance injected)}}{cn \text{ (concentration of test substance in a sample)}}$$

N, the net amount of activity administered to the patient, is obtained by counting the total radioactivity in the dose syringe and subtracting the residual uninjected radioactivity while background is simultaneously corrected for. The net injected activity is then stored in a scalar memory circuit. The cn is obtained from the simultaneous measurements of fixed volumes of samples of blood taken before and after injection of I^{131}-tagged albumin while the machine again corrects for background activity. (Volumetric errors are minimized by filling the containers for samples taken before and after injection of I^{131}-tagged albumin well beyond a point detectable by the scintillation counter, thereby creating a constant effective volume.) During this step, the instrument is in an integral preset count mode. The net difference in counting rates of the samples taken before and after injection of I^{131}-tagged albumin is applied by subtraction for the interval necessary to erase the scalar load (net injected activity). When the scalar load is exhausted, a meter which functions as a timer stops. The timer is calibrated in milliliters of blood volume and is read directly off a meter scale. Since the counting interval is relatively short, the sedimentation rate does not appear to be a factor. The principles of design and operation of this instrument, including the accuracy of its performance, were evaluated in detail by Williams and Fine[27] in 1961.

In each instance, hematocrits were determined in duplicate from the samples taken before and after in-

Table I. Blood volume and hematocrit in 75 patients with normal term pregnancy and in 28 patients six weeks post partum

	Blood volume (L.)	*Blood volume (c.c./Kg.)*	*Hematocrit (%)*
Term pregnancy (75 patients)			
Range	4.37-8.50	56.8-107.1	27.0-45.0
Mean	5.95	83.3	35.2
S.D.	±0.83	±12.5	±3.6
Six weeks post partum (28 patients)			
Range	3.22-5.62	57.8-84.3	35.3-48.0
Mean	4.12	71.7	40.8
S.D.	±0.51	±6.5	±3.1

Table II. Maternal blood volume and the weight of the products of conception

Weight of products of conception (newborn infant and placenta) (Kg.)	*Blood volume*	
	c.c./Kg.	*L.*
<3.50	82.5	5.63 ± 0.55
3.50-3.99	84.4	5.62 ± 0.57
4.00-4.49	81.3	6.03 ± 0.64
>4.50	85.8	6.49 ± 0.97
Twins	92.9	6.66 ± 1.37

jection of I^{131}-tagged albumin by the microtechnique after five minutes of centrifugation at 12,500 r.p.m. No correction was made in determining hematocrit for plasma trapped in the column of red cells. Since sampling sites were constant and tourniquets were not used, the relative value of the hematocrit was assumed to be valid.

Results

A total of 75 term pregnant women were studied. Table I shows the range, mean, and one standard deviation of blood volume, expressed in both liters and cubic centimeters per kilogram, and the per cent hematocrit for all patients. For comparison, the values found at six weeks post partum are also included. There was a mean increment in blood volume at term pregnancy of 1.83 L. or 44 per cent. When expressed in cubic centimeters per kilogram, the increment was 11.6 c.c. per kilogram or 16 per cent. On the other hand, the hematocrit was 5.6 per cent lower at term pregnancy than at six weeks post partum in this group of patients—a decline of 14 per cent.

Table II summarizes the relationship of blood volume to the weight of the products of conception. There was no statistically significant correlation between blood volume in liters or blood volume in cubic centimeters per kilogram and the combined weight of the neonate and placenta. However, blood volume (in liters) tended to rise with increasing weight of the products of conception and was largest in twin gestations (6.66 L.). Table III demonstrates a similar relationship between total circulating blood volume (liters) and the weight of the newborn infant. The wide range of values in blood volume in all groups precluded statistical significance, but the trends were, nonetheless, consistent. The heterogeneity of the patient population studied may, in part, account for this lack of statistical correlation.

Table III. Maternal blood volume and weight of the newborn

Newborn weight (Kg.)	*Blood volume (L.)*		
	Range	*Mean*	*S.D.*
<3.25	4.37-6.95	5.64	±0.063
3.25-3.75	4.63-7.28	5.99	±0.72
>3.75	4.75-8.50	6.45	±1.06
Twins	5.71-8.77	6.66	±1.37

Table IV. Blood volume and maternal weight at term

	No. of patients	*Blood volume (c.c./Kg.)*	*Range (c.c./Kg.)*
Single pregnancy (all)	75	83.3	56.8-107.1
Weight			
>90 Kg. (198 pounds)	8	68.2	56.8-74.0
75 Kg. (165 pounds)-90 Kg.	22	80.2	60.4-101.7
60 Kg. (132 pounds)-75 Kg.	33	85.2	66.0-109.8
<60 Kg.	12	94.3	82.3-106.9

As in the nonpregnant subject, blood volume appears to correlate with lean body mass. Table IV demonstrates this relationship at term. As expected, with increasing maternal weight, there was a decline in blood volume when expressed as cubic centimeters per kilogram. The trend is obvious, but the wide range and overlap in values again precluded statistical significance.

Table V depicts intrapartum and postpartum blood volume and hematocrit changes in patients delivered of their infants vaginally and by cesarean section. The mean decline in blood volume in 26 patients delivered vaginally was 0.61 L. at one hour post partum. The hematocrit remained essentially unchanged. In patients delivered by cesarean section, the blood volume declined by an average of 1.03 L. at one hour post partum. Again, the hematocrit remained unchanged. By the third postpartum day, the mean blood volume

Table V. Intrapartum and postpartum blood volume and hematocrit changes

		Postpartum				
	Predelivery	*10 min.*	*1 hour*	*Day 1*	*Day 3*	*Day 5*
Vaginal delivery (26 patients)						
Blood volume (L.)						
Range	4.85-7.80	4.51-6.85	4.12-6.55	4.15-6.14	4.02-5.92	
Mean	6.0	5.57	5.39	5.09	5.03	
S. D.	±0.76	±0.63	±0.70	±0.68	±0.56	
Hematocrit (%)						
Range	27-40.5	29-41	29-39.5	29-40.5	31-42.5	
Mean	34.9	35.8	35.1	35.9	36.7	
S. D.	±2.9	±2.9	±2.9	±2.8	±3.1	
Cesarean section (34 patients)						
Blood volume (L.)						
Range	4.37-8.50	3.64-7.05	3.07-6.85	3.57-6.44	3.36-6.35	3.56-6.75
Mean	5.92	5.07	4.89	4.94	4.96	4.78
S. D.	±0.88	±0.74	±0.76	±0.75	±0.82	±0.69
Hematocrit (%)						
Range	28.5-42.0	28-42	28.5-40.5	29.0-41.0	28.0-39.0	27.0-39.5
Mean	34.8	34.5	34.3	34.0	33.2	32.8
S. D.	±3.6	±3.5	±3.7	±2.7	±3.4	±3.8

was 5.03 L., a decrease of 0.97 L. from the predelivery value in patients delivered vaginally. The comparable figure for patients delivered surgically was 4.96 L. for a 0.96 L. decline. This remarkable similarity between the two groups was unanticipated. The hematocrit increased by 5.2 per cent following vaginal delivery but declined following cesarean section by 5.8 per cent.

At six weeks post partum, follow-up studies in 28 patients showed that there was no difference in blood volume between the two groups but that the hematocrit was consistently lower in those patients delivered by cesarean section. Iron was routinely prescribed for six weeks post partum, but no attempt was made to determine whether or not it was taken with any degree of regularity.

Comment

The mean term blood volume of 5.05 L. found in this study agrees very well with the results obtained by many others.[2, 3, 17–19, 21, 26] Quinlivan and Brock,[19] in 1970, reported a mean blood volume of 5.475 L. at term (they also utilized I^{131}-tagged albumin as the indicator), closely resembling the value reported here. On the other hand, Pritchard,[18] using Cr^{51}-labeled red blood cells, found a mean blood volume of 4.182 L. in 50 patients with single pregnancies near term. The differences in technique could account for the major portion of this discrepancy, as extravascular migration of the I^{131}-labeled albumin tends to overestimate volume. However, more important for comparative purposes, the per cent changes are comparable in both studies. Pritchard found a rise of 48 per cent from nonpregnant values, while in this study an increment of 44 per cent occurred. In 30 twin pregnancies, he found the blood volume to be 5.82 L., which constituted a rise of 51 per cent over nonpregnant levels. In six twin pregnancies in this study, the increment was 61 per cent.

When blood volume is expressed in cubic centimeters per kilogram, the mean value in this study of 83.3 c.c. per kilogram again falls well within the range reported by others in the literature—73 to 96 c.c. per kilogram.[2, 10, 14, 16, 20, 21] As previously mentioned, there are many factors that contribute to the wide range of values in the literature. Hytten and Paintin[12] found that the rise in plasma volume during pregnancy correlated directly with fetal weight in single primigravid patients. On the other hand, Rovinsky and Jaffin[20] found a positive relationship between the per cent increase in plasma volume near term and the total placental weight at delivery. The present investigation shows a general correlation between total blood volume (liters) and both the weight of the products of conception and the neonatal weight. Because of the wide range in values, this relationship is not statistically significant. However, it would seem reasonable to assume that such a relationship does exist because large women generally have large babies at term and total blood volume (liters) correlates roughly with body mass. In addition, large babies have large placentas, which, in turn, cause a greater increment in uterine size and determine the capacity of the large vascular compartment surrounding the uterus. Undoubtedly, there are a multitude of other factors that contribute to the hypervolemia of pregnancy. Most are not clearly understood, but the hormonal alterations that accompany pregnancy must be important. Whatever the

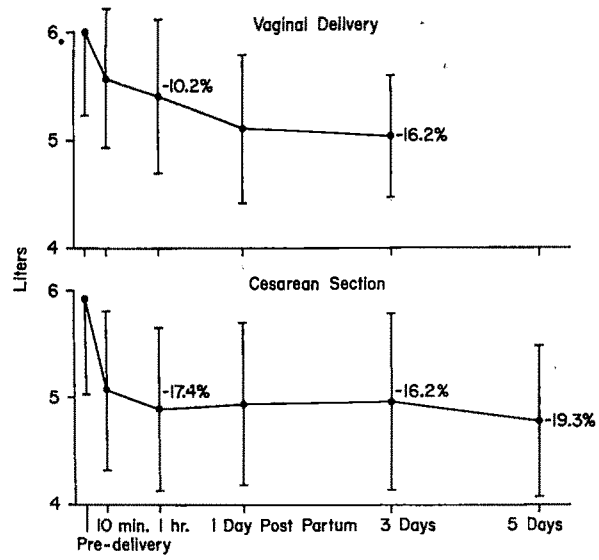


Fig. 1. Postpartum change in blood volume in patients delivered vaginally and by cesarean section (mean ± one standard deviation).

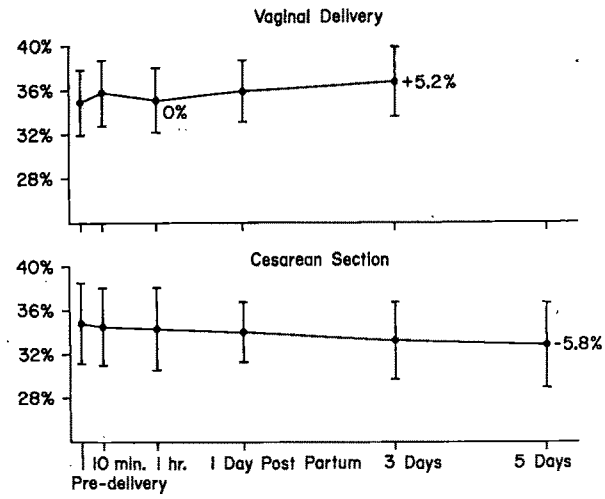


Fig. 2. Postpartum change in hematocrit in patients delivered vaginally and by cesarean section (mean ± one standard deviation).

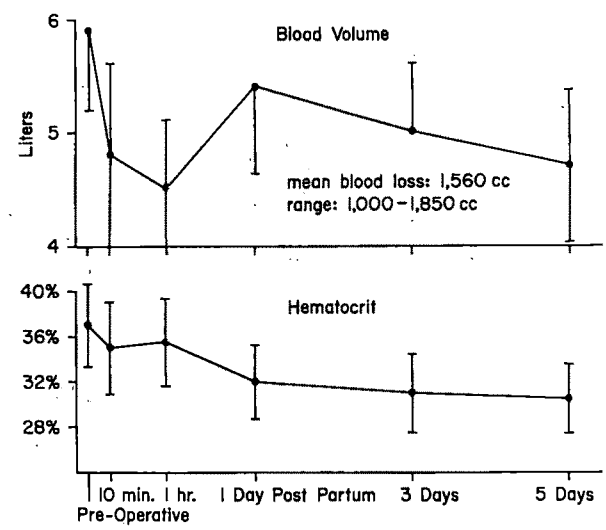


Fig. 3. Blood volume and hematocrit changes in patients undergoing cesarean section resulting in blood volume loss greater than 20 per cent of total volume (mean ± one standard deviation).

mechanisms, it is clear that the hypervolemia acts as a safeguard against maternal blood loss at delivery.

Figs. 1 and 2 graphically depict per cent changes in blood volume and hematocrit from predelivery control values to postpartum Day 3 in patients delivered vaginally and to postpartum Day 5 in those delivered surgically. In patients undergoing vaginal delivery, the decline in blood volume was progressive through the third postpartum day. In patients delivered by cesarean section, a rapid decline in blood volume occurred as early as one hour postpartum and then remained remarkably constant through the fifth postpartum day. Most noteworthy is the fact that the per cent of blood volume loss was exactly the same in both groups by the third postpartum day (16.2 per cent). The only difference was in the hematologic parameters, as there was a rise in hematocrit of 5.2 per cent in the patients delivered vaginally and a concurrent fall of similar magnitude (5.8 per cent) in those delivered surgically. The latter most likely represents a mild compensatory hemodilution attributable to the more extensive blood loss encountered at cesarean section.

In this study, there was no evidence of any significant rise in blood volume during the early puerperium, as has been suggested by others[5, 13, 15] and attributed to the mobilization of interstitial fluid. However, if one carefully peruses the studies supporting this concept, it becomes apparent that the evidence is neither convincing nor conclusive. One group of investigators[5] admitted technical difficulties with estimating plasma volume, and their reported results are based on very few patients. Landesman and Miller[13] studied plasma volume in a small heterogeneous group of 20 patients, of whom five had toxemia of varying severity and one had severe anemia. Of the remaining 14, the authors stated that "approximately one-half showed little change." Neither of these two studies attempted to relate the very important parameter of blood loss at delivery to puerperal plasma volume changes. McLennan and Lowenstein[15] measured blood volume in a larger number of patients (61), but studies were repeated on two occasions within three days of delivery in only 17 patients and at approximately 24 and 48 hours in only 14

Table VI. Postpartum blood volume and hematocrit changes with comparison of Pritchard's[18] data and those of this series

Series	No. of patients	Before delivery		1-10 hr. post partum				3-7 days post partum			
		Blood volume (L.)	Hematocrit (%)	Blood volume		Hematocrit		Blood volume		Hematocrit	
				(L.)	Per cent Δ	(%)	Per cent Δ	(L.)	Per cent Δ	(%)	Per cent Δ
Vaginal delivery											
Pritchard	8	5.04	38.0	4.51	−10.0	39.0	+3.0	4.18	−17.0	41.0	+8.0
This series	26	6.00	34.9	5.39	−10.2	35.1	+0.6	5.03	−16.2	36.7	+5.2
Cesarean section											
Pritchard*	8	4.99	35.0	3.53	−29.0	35.5	+1.0	3.53	−29.0	33.5	−5.8
This series	34	5.92	34.8	4.89	−17.4	34.3	−1.4	4.78	−19.3	32.8	−5.8

*Includes patients undergoing cesarean hysterectomy.[18]

patients. Careful examination of the data in these 14 patients shows a mean blood volume of 5.71 L. before delivery, 4.61 L. at 24 hours post partum, and 4.93 L. at 48 hours post partum. There is no statistically significant difference between the values at 24 and 48 hours, and the authors state that, in six patients, "the volumes appeared to continue downward." Unfortunately, neither hemoglobin nor hematocrit values were given.

It is conceivable that a transient rise in plasma volume 48 hours post partum could have been overlooked in the present investigation, but it would seem incongruous that the timing of this increment would have been such that it occurred entirely undetected. The findings of Pritchard[18] support my contention that there normally is no transient rise in blood volume or plasma volume in the early puerperium. Under normal circumstances and with good renal function, any absorbed extracellular fluid would be rapidly excreted by the kidney without detectable volume changes. It has been shown that rapid infusion of large volumes of electrolyte solutions disappear quickly from the intravascular space in normal subjects by redistribution through the extravascular space and excretion through the kidneys.[1, 4, 27] In patients who experience excessive blood loss at delivery, a transient rise in plasma volume might occur in the early puerperium. Under these circumstances, hemodilution results from the body's attempt to compensate for the large volume loss. Therefore, it is critical to measure blood loss at delivery if one is to evaluate correctly postpartum volume changes.

I have studied five patients delivered by cesarean section who had a decline in blood volume greater than 20 per cent of the total by one hour post partum. Fig. 3 shows the compensatory hemodilution that occurs and the rise in blood volume measured at 24 hours post partum as compared to one hour following delivery. The expected drop in hematocrit can readily be seen as well. These changes do not occur when the blood loss is equivalent to or less than the reduction in vascular capacity which accompanies normal delivery.

When comparing the per cent change, Pritchard[18] recorded a 10 per cent decline one to 10 hours post partum compared to a 10.2 per cent decline in this study and a 17 per cent change three to seven days post partum compared to a 16.2 per cent change in this study. The increments in hematocrit are also comparable. He noted a rapid loss in blood volume within hours after cesarean section delivery, followed by a stable blood volume over the next several days post partum, again closely paralleling the findings in this study. The larger blood loss reported by Pritchard at cesarean section is a reflection of the fact that some of his patients underwent cesarean section plus hysterectomy (Table VI).

It is clear from this investigation and a review of the literature that pregnant women tolerate a surprisingly large blood loss at delivery without suffering any ill effects. The external blood loss accounts for all of the measured decline in blood volume,[9, 19] and there is no evidence that supports the previously suggested theory of whole-blood sequestration in the early puerperium. Since all evidence points to an average blood loss of 500 c.c. or more at vaginal delivery and 1,000 c.c. or more at cesarean section, should not our definition of postpartum hemorrhage be revised? Postpartum hemorrhage should be realistically defined as blood loss from vaginal delivery that results in a decline in hematocrit 24 hours post partum. This clearly indicates blood loss in excess of the protective and physiologic hypervolemia of pregnancy. For years we have grossly underestimated parturition blood loss, and present data should direct our attention to a measurable and meaningful parameter rather than the antiquated "educated" guess.

REFERENCES

1. Askrog, V.: Br J. Anaesth. **38:** 455, 1966.
2. Berlin, N. I., Goetsch, C., Hyde, G. M., and Parsons, R. J.: Surg. Gynecol. Obstet. **97:** 173, 1953.
3. Bhatt, J. R.: Obstet. Gynecol. **26:** 243, 1965.
4. Boyan, C. P., Underwood, P. S., and Howland, U. S.: Anesthesiology **27:** 279, 1966.
5. Brown, E., Sampson, J. J., Wheeler, E. O., Gundelfinger, B. F., and Giansiracusa, J. E.: Am. Heart. J. **34:** 311, 1947.
6. Butler, E. B.: J. Obstet. Gynaecol. Br. Commonw. **75:** 497, 1968.
7. Chesley, L. C.: AM. J. OBSTET. GYNECOL. **112:** 440, 1972.
8. Chesley, L. C., and Duffus, G. M.: J. Obstet. Gynaecol. Br. Commonw. **78:** 406, 1971.
9. DeLeeuw, N. K. M., Lowenstein, L., Tucker, E. C., and Dayal, S.: AM. J. OBSTET. GYNECOL. **100:** 1092, 1968.
10. Dieckmann, W. J., and Wegner, C. R.: Arch. Intern. Med. **53:** 71, 1934.
11. Gahres, E. E., Albert, S. N., and Dodek, S. M.: Obstet. Gynecol. **19:** 455, 1962.
12. Hytten, F. E., and Paintin, D. B.: J. Obstet. Gynaecol. Br. Commonw. **70:** 402, 1963.
13. Landesman, R., and Miller, M. M.: Obstet. Gynecol. **21:** 40, 1963.
14. Lund, C. J., and Donovan, J. C.: AM. J. OBSTET. GYNECOL. **98:** 393, 1967.
15. McLennan, C. E., and Lowenstein, J. M.: Stanford Med. Bull. **17:** 152, 1959.
16. Miller, J. R., Keith, N. M., and Rowntree, L. G.: J. A. M. A. **65:** 779, 1915.
17. Osofsky, H. J., and Williams, J. A.: AM. J. OBSTET. GYNECOL. **88:** 396, 1964.
18. Pritchard, J. A.: Anesthesiology **26:** 393, 1965.
19. Quinlivan, W. L. G., and Brock, J. A.: AM. J. OBSTET. GYNECOL. **106:** 843, 1970.
20. Rovinsky, J. J., and Jaffin, H.: AM. J. OBSTET. GYNECOL. **93:** 1, 1965.
21. Statzer, D. E.: Obstet. Gynecol. **14:** 37, 1959.
22. Ueland, K., Akamatsu, T. J., Eng M., Bonica, J. J., and Hansen, J. M.: AM. J. OBSTET. GYNECOL. **114:** 775, 1972.
23. Ueland, K., Gills, R. E., and Hansen, J. M.: AM. J. OBSTET. GYNECOL. **100:** 42, 1968.
24. Ueland, K., and Hansen, J. M.: AM. J. OBSTET. GYNECOL. **103:** 8, 1969.
25. Ueland, K., Hansen, J., Eng, M., Kalappa, R., and Parer, J. T.: AM. J. OBSTET. GYNECOL. **108:** 615, 1970.
26. Venning, E. H., Dyrenfurth, I., Lowenstein, L., and Beck, J. J.: J. Clin. Endocrinol. Metab. **19:** 403, 1959.
27. Williams, J. A., and Fine, J.: N. Engl. J. Med. **264:** 842, 1961.
28. Wollman, S. B., and Marx, G. F.: Anesthesiology **29:** 374, 1968.

Serum human chorionic gonadotropin levels throughout normal pregnancy

GLENN D. BRAUNSTEIN, M.D.
JOAN RASOR, M.A.
DONALD ADLER, M.D.
HAL DANZER, M.D.
MACLYN E. WADE, M.D.
Los Angeles, California

Human chorionic gonadotropin (hCG) levels were measured in the sera of 443 pregnant women by the beta-hCG radioimmunoassay in order to determine if the third-trimester secondary peak in hCG levels observed by less specific immunoassays was due to cross-reacting substances. hCG was detected as early as six days after presumed conception and peaked between 56 and 68 days, with a nadir at 18 weeks. No secondary rise in hCG levels was demonstrated, indicating that the nonspecific hCG immunoassays give spuriously high values for hCG during the last trimester of pregnancy. (AM. J. OBSTET. GYNECOL. 126: 678, 1976.)

IN 1938, BOYCOTT and Rowlands[1] first described the quantitative pattern in serum of human chorionic gonadotropin (hCG) secretion throughout normal pregnancy. Since then, numerous bioassays and immunologic methods have been utilized to measure hCG in the serum of pregnant women. The qualitative aspects of hCG secretion during the first two trimesters are remarkably similar between reports, with peak levels of hCG being found between 8 and 12 weeks after the last menstrual period. However, the hCG secretory pattern during the last trimester has varied according to the method used for measuring the molecule. Bioassays generally show a persistently low level of hCG in the serum that does not differ significantly from those found in the latter part of the second trimester,[2] while immunoassay techniques have usually demonstrated a secondary rise in hCG during the last trimester.[3, 4] These discrepancies may reflect the presence of immunologically active, but biologically inactive, fragments or subunits of hCG or cross-reaction with other glycoprotein hormones. In order to better define the qualitative and quantitative aspects of hCG secretion, we have examined the hCG content of sera from 443 women with uncomplicated pregnancies by using a radioimmunoassay for hCG which does not significantly cross react with the other glycoprotein hormones or their alpha subunits.

From the Departments of Medicine and Obstetrics and Gynecology, Cedars-Sinai Medical Center, and the University of California Los Angeles School of Medicine.

Supported in part by United States Public Health Service Grant 5-S01 RR05468.

Received for publication October 14, 1975.

Revised March 15, 1976.

Accepted April 9, 1976.

Reprint requests: Dr. Glenn D. Braunstein, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90048.

Material and methods

Specimens. Samples of 7 ml. of blood were obtained from 443 women with normal, uncomplicated pregnancies by venipuncture. The serum was rapidly separated from the clot and frozen at −20° C. until use. Dating of the serum sample was accomplished by utilizing the first day of the last menstrual period as Day 1 of pregnancy. When such information was not available, dating of the specimen was based upon the date of delivery of a normal term infant, with the assumption that the period of gestation was 40 weeks.

hCG measurements. The double-antibody beta radioimmunoassay (RIA) for hCG previously described by Vaitukaitis and associates[5] was utilized to measure hCG in the serum samples. In this assay an antisera generated against the beta subunit of hCG is used. It is specific for hCG and its beta subunit in the presence of physiologic amounts of human luteinizing

hormone (hLH).[5] There is no significant cross-reaction with the alpha subunit of hCG (0.4 per cent) or with the other glycoprotein hormones. The original RIA has been modified in that ^{125}I-hCG rather than ^{125}I–hCG-beta subunit is utilized for tracer purposes without a change in the assay's sensitivity or specificity. A highly purified preparation of hCG (CR 115, 5,000 I.U. per milligram by radioimmunoassay relative to the Second International Standard for hCG) was used as the standard.

hLH/hCG measurements. An antiserum raised against hLH which does not discriminate between hLH and hCG was supplied by the Hormone Distribution Officer, National Institute of Arthritis, Metabolism, and Digestive Diseases. It was utilized in a double-antibody RIA with ^{125}I-hCG used as a trace and a purified preparation of hCG (CR 115) used as the standard. The alpha subunit of hCG cross reacts with intact hCG approximately 1 per cent in this assay, while hLH cross reacts 100 per cent.* Results were expressed in terms of International Units per milliliter, relative to the Second International Standard for hCG.

Statistical analyses. The statistical methods of Rodbard and Frazier[6] were used to evaluate each RIA. The differences between correlated means were compared by Student's t test. A least-squares linear regression analysis between the hCG levels obtained from the beta-subunit RIA and those obtained from the same samples by the nonspecific hLH/hCG RIA was carried out on a Compucorp calculator, Model 145-E Statistician.

Results

The mean values for hCG from the third week after the last menstrual period through parturition are shown in Table I and Fig. 1. hCG was detected as early as six days after presumed ovulation (Day 14) with peak levels being reached at 8 to 8.5 weeks. The concentration dropped rapidly after 11½ weeks, reached a nadir at 18 weeks, and remained low throughout the rest of gestation. No significant difference in mean concentration was detected between sequential weeks from 18 to 40 weeks of gestation. Even when the values between 18 and 26½ weeks were grouped and compared to those between 27 and 40 weeks, no significant difference was found ($P < 0.4$).

A highly significant linear correlation was found between the hCG concentration in 33 samples of pregnancy sera determined by both the beta-subunit RIA and the less-specific hLH/hCG RIA ($r = 0.94$; $p < 0.001$). However, the levels of hCG measured were consistently greater by the hLH/hCG RIA than by the beta-subunit assay. A comparison of the separate linear regression analyses for the hCG levels in the first and second trimesters versus the third trimester revealed a steeper slope during the third trimester. This configuration indicated that relative to the beta-subunit RIA the hLH/hCG RIA measured more immunoreactive material in the thrid trimester than in the first two trimesters.

*Braunstein, G. D.: Unpublished observations.

Table I. Mean serum hCG levels throughout normal gestation as determined by the beta-hCG RIA gestational dates are based on the first day of the last menstrual period (LMP).
No. = Number of patients in each group.

Weeks after LMP	*No.*	*Mean (I.U./ml.)*	*S.E.M.*
3-3.5	11	0.0216	0.0057
4-4.5	18	0.353	0.089
5-5.5	19	2.27	0.39
6-6.5	12	6.64	1.16
7-7.5	6	13.61	2.74
8-8.5	6	46.83	4.71
9-9.5	3	44.71	3.69
10-10.5	9	37.75	5.42
11-11.5	12	38.36	8.10
12-12.5	18	28.28	3.64
13-13.5	9	30.73	2.84
14-14.5	14	24.76	3.75
15-15.5	17	19.01	1.57
16-16.5	8	16.81	2.79
17-17.5	14	15.26	2.55
18-18.5	17	10.01	1.20
19-19.5	12	11.05	1.99
20-20.5	9	9.06	1.08
21-21.5	13	10.66	2.09
22-22.5	8	10.10	2.47
23-23.5	9	5.89	0.88
24-24.5	15	9.85	1.32
25-25.5	14	9.48	1.70
26-26.5	14	5.48	0.97
27-27.5	18	8.17	1.83
28-28.5	9	14.34	4.01
29-29.5	7	7.56	2.37
30-30.5	10	7.40	1.93
31-31.5	7	12.07	3.41
32-32.5	13	12.10	4.12
33-33.5	12	11.52	2.64
34-34.5	11	8.65	1.89
35-35.5	17	12.00	2.67
36-36.5	5	7.24	1.38
37-37.5	9	6.16	1.41
38-38.5	15	11.89	1.79
39-39.5	19	10.02	1.08
40-40.5	4	5.30	3.13

Comment

hCG is a glycoprotein hormone composed of two dissimilar subunits, the alpha and beta subunits.[7] The alpha subunit of hCG is virtually identical to the alpha subunit of hLH physiochemically, structurally, and

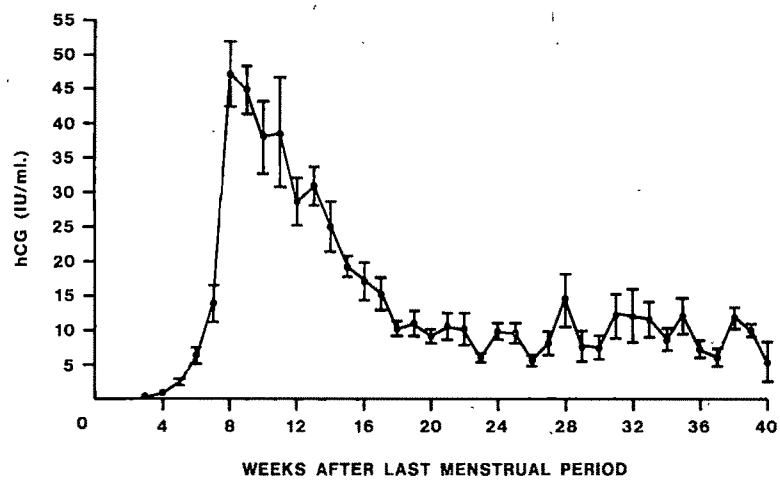


Fig. 1. Mean serum hCG levels throughout normal pregnancy. Arithmetical scale used on ordinate. Bars represent ±1 standard error of the mean.

immunologically, while the beta subunit of hCG differs from the beta subunit of hLH in that the beta subunit of hCG contains 30 amino acid residues in excess of that found in the beta subunit of hLH.[8] Because of the close homology between these two molecular species, antisera generated against either intact hCG or intact hLH would be expected to demonstrate immunologic cross-reactivity between these two molecules, an observation which has been repeatedly confirmed.[9] It was with this in mind that an RIA was developed which utilized the purified beta subunit of hCG for antigenic purposes. The antisera directed against the beta subunit of hCG did not show significant cross-reaction with physiologic concentrations of intact hLH[5] or with the alpha subunit of hCG.[10]

The secretion of hCG during normal pregnancies has been studied for many years. The reports in which hCG was measured by bioassay methods are remarkably similar qualitatively.[1, 2] By these methods, hCG is generally detected as early as 24 days after the last menstrual period. Peak levels of serum hCG are reached between the eighth and twelfth weeks of gestation. Thereafter, the levels decline, reaching a nadir in the second trimester where they remain until parturition. Initial immunoassay methods for measuring hCG utilized hemagglutination-inhibition or complement-fixation techniques.[3, 11] In the last ten years, a number of radioimmunoassays have been used to determine serum levels of hCG.[4] All these immunologic methods were hampered by the above-noted cross-reaction between hCG and hLH, since the immunogen used was intact hCG or hLH. The majority of these immunoassays were quite similar quantitatively, with peak levels of hCG again having been detected between 8 and 12 weeks, followed by a rapid decline to low levels during the second trimester. The immunologic methods differed from the bioassay results in that a secondary peak of hCG was detected during the third trimester by the immunoassays. The discrepancy could be explained by the secretion late in pregnancy of an immunologically active, but biologically inactive, form of hCG, the concomitant overproduction of the biologically inactive free alpha and/or beta subunits of hCG, or by the presence in the blood of significant levels of other cross-reacting glycoproteins.

There exists a great deal of evidence that hCG secreted during pregnancy is, indeed, heterogeneous. Vaitukaitis[12] has demonstrated that a "big" hCG is present in placental extracts, along with the immunoreactive forms that are usually found in the serum and urine. Other investigators have shown heterogeneity in the molecular composition of the hCG found in urine during pregnancy, due to differences in the content of sialic acid.[13] Progressive removal of the sialic acid moiety from hCG leads to a marked reduction of the biological activity with maintenance of the immunoreactivity.[14] Since hCG containing no sialic acid is immunologically active in the beta-hCG RIA, the lack of a third-trimester secondary rise in hCG levels, when measured by this assay, suggests that excessive secretion of biologically inactive, partially sialyated forms of hCG does not occur.

Studies by Vaitukaitis[12] on placental extracts and Franchimont and co-workers[15] on placental organ cultures, have shown that the normal human placenta contains and secretes large amounts of the free alpha subunit of hCG with little or no concomitant storage or secretion of the free beta subunit. Ashitaka and associ-

ates[16] have demonstrated that the placenta secretes increasing amounts of free alpha subunits as pregnancy progresses, while the serum levels of the free beta subunit of hCG remain low throughout gestation. However, the data from Ashitaka and co-workers[16] indicate that only 0.4 I.U. per milliliter of the hCG measured in the nonspecific hLH/hCG RIA during the last trimester could be accounted for by the cross-reaction of the alpha and beta subunits of hCG in this assay.

Although no information is available concerning hLH levels in maternal serum throughout pregnancy, it is unlikely that elevated levels of this hormone are responsible for the third-trimester rise in immunoreactive hCG activity, since it would be expected that the bioassays could also detect this substance.

We are thus unable to satisfactorily explain the qualitative differences in the pattern of hCG secretion throughout pregnancy that are found when bioassays and nonspecific immunoassays are used to measure the hormone. The pattern of hCG secretion determined by the beta-hCG RIA is similar to that obtained by bioassays. This finding, together with the observation that the less specific hLH/hCG RIA consistently overestimates the level of hCG in serum in comparison to those obtained in the beta-hCG RIA, indicates that nonspecific hCG immunoassays are measuring other substances in addition to hCG thoughout pregnancy, resulting in spuriously high values for hCG, especially during the last trimester.

We acknowledge the technical assistance of Mr. G. Van Scarboro and Mr. Ira Vogel and the secretarial assistance of Anita Leonard. The pruified hCG and anti-beta subunit serum were supplied by the Hormone Distribution Officer, National Institute of Child Health and Human Development and National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland.

REFERENCES

1. Boycott, M., and Rowlands, I. W.: The biological nature and quantitative variation of the gonadotropic activity of pregnant women's serum, Br. Med. J. **1:** 1097, 1938.
2. Albert, A., and Berkson, J.: A clinical bio-assay for chorionic gonadotropin, J. Clin. Endocrinol. Metab. **11:** 805, 1951.
3. Brody, S., and Carlstrom, G.: Immuno-assay of human chorionic gonadotropin in normal and pathologic pregnancy, J. Clin. Endocrinol. Metab. **22:** 564, 1952.
4. Varma, K., Larraga, L., and Selenkow, H. A.: Radioimmunoassay of serum human chorionic gonadotropin during normal pregnancy, Obstet. Gynecol. **37:** 10, 1971.
5. Vaitukaitis, J. L., Braunstein, G. D., and Ross, G. T.: A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone, Am. J. Obstet. Gynecol. **113:** 751, 1972.
6. Rodbard, D., and Frazier, G. R.: Radioimmunoassay Data Processing, ed. 2, Springfield, Virginia, 1973, National Technical Information Service.
7. Canfield, R. E., Morgan, F. J., Kammerman, S., Bell, J. J., and Agosto, G. M.: Studies of human chorionic gonadotropin, Recent Prog. Horm. Res. **27:** 121, 1971.
8. Bahl, O. P., Carlson, R., Bellisario, R., and Swaminathan, N.: Human chorionic gonadotropin: Amino acid sequence of alpha and beta subunits, Biochem. Biophys. Res. Commun. **48:** 416, 1972.
9. Paul, W. E., and Ross, G. T.: Immunologic cross-reaction between human chorionic gonadotropin and human pituitary gonadotropin, Endocrinology **75:** 352, 1964.
10. Vaitukaitis, J. L., and Ross, G. T.: Antigenic similarity among the human glycoprotein hormones and their subunits, *in* Saxena, B., Gandy, H., and Beling, C., editors: New York, John Wiley & Sons, Inc., 1972, pp. 435-443.
11. Mishell, D. J., Jr., Wide, L., and Gemzell, C. A.: Immunologic determination of human chorionic gonadotropin in serum, J. Clin. Endocrinol. Metab. **23:** 125, 1963.
12. Vaitukaitis, J. L.: Changing placental concentrations of human chorionic gonadotropin and its subunits during gestation, J. Clin. Endocrinol. Metab. **38:** 255, 1974.
13. Van Hell, H., Goverde, B. C., Schuurs, A. H. W. M., DeJager, E., Matthijsen, R., and Homan, J. D. H.: Purification, characterization and immunochemical properties of human chorionic gonadotropin, Nature **212:** 261, 1966.
14. Van Hall, E. V., Vaitukaitis, J. L., Ross, G. T., Hickman, J. W., and Ashwell, G.: Immunologic and biologic activity of hCG following progressive desialylation, Endocrinology **88:** 456, 1971.
15. Franchimont, P., Gaspard, U., Reuter, A., and Heynen, G.: Polymorphism of protein and polypeptide hormones, Clin. Endocrinol. **1:** 315, 1972.
16. Ashitaka, Y., Nishimura, R., Futamura, K., Ohashi, M., and Tojo, S.: Serum and chorionic tissue concentrations of human chorionic gonadotropin and its subunits during pregnancy, Endocrinol. Jap. **21:** 547, 1974.

Uterine activity in the multiparous patient

JAMES R. HUEY, JR., LIEUTENANT COLONEL, USAF, MC
ALEXANDER AL-HADJIEV, M.D.
RICHARD H. PAUL, M.D.
Los Angeles, California

There were 149 parous patients with normal cervical dilatation patterns studied. The purpose was to quantitate and characterize uterine activity in a group of multiparous patients with normal labor using our present on-line method and to evaluate our method against previous work done on uterine activity. A mean total of 5,299 uterine activity units (UAU) was required to progress from 4 cm. through delivery. In the patients receiving oxytocin 5,907 UAU were required and 4,498 UAU for those not receiving oxytocin. Of the total uterine work from 4 cm. to delivery, 49.4 per cent was required to progress from 4 to 6 cm., 38.7 per cent to progress from 6 to 10 cm., and 11.9 per cent for the second stage. This study establishes in a quantitative way, using on-line methods, the patterns of uterine activity expended by the parous patient in normal labor and can be compared to previous off-line and manual evaluations. These data can be compared with the on-line observations previously made in a primiparous group, and will be fundamental to automated evaluations including definitions of abnormal labor.
(AM. J. OBSTET. GYNECOL. 126: 682, 1976.)

SEVERAL CENTERS are concurrently utilizing on-line computer analysis to evaluate fetal heart rate and uterine activity.[1, 2] Several factors have brought about this renewed effort to evaluate uterine activity, including increased availability of instrumentation. There are now widespread clinical use and observations with electronic monitoring of uterine activity, showing its highly variable nature from patient to patient and in the same patient. These observations again raise the questions of the relationship between uterine activity and the "classic obstetric definitions of labor" which are profuse and frequently confusing.[3]

The clinical assessment of uterine activity is expressed in terms of cervical dilatation, effacement, and descent, i.e., progress in labor. In most patients this appraisal is satisfactory, but provides no quantitative measurement in dealing with abnormal labors. Previous methods of measuring uterine activity used manual off-line techniques. A widely used method has been employed using Montivideo units, which are determined by multiplying the average intensity rise (in millimeters of mercury) of the contractions times the frequency in 10 minutes.[4] Another similar method adds the additional variable of contraction duration and the final calculation is expressed in Alexandria units.[5] All manual methods are time consuming and inconvenient in that they are off-line and must be retrospectively calculated.

Also, most reported studies utilizing computer evaluation of uterine activity produce data off-line and therefore not available for immediate clinical use. Findings from our study can be compared to past reports of both manual and off-line computer evaluation of uterine activity.

On-line computer analysis of the intrauterine pressure recording has the advantage of being rapid and accurate, with immediately available results. A simple on-line technique for measuring the total area under the uterine pressure curve including both tone and contractions has been previously reported.[6] This inexpensive system[7] employs a voltage controlled oscillator (VCO) which integrates the total area under the uterine pressure curve and provides a numerical print-out of the uterine activity expressed in Torr per minutes every 2½ minutes.

From the Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine of the Los Angeles County–University of Southern California Medical Center.

Received for publication March 29, 1976.

Accepted April 9, 1976.

Reprint requests: James R. Huey, Jr., M.D., Women's Hospital, Room 5K-22, 1240 N. Mission Rd., Los Angeles, California 90033.

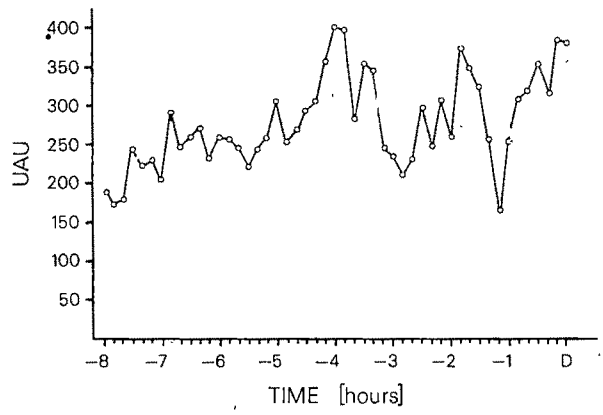


Fig. 1. The nonaccumulative UAU per 10 minutes from 4 cm. to delivery in a 25-year-old woman, gravida 5, para 2, Ab 2, induced at 37 weeks because of Rh disease. This type of individual calculation was performed on each patient and shows the marked variation in the 10 minute values.

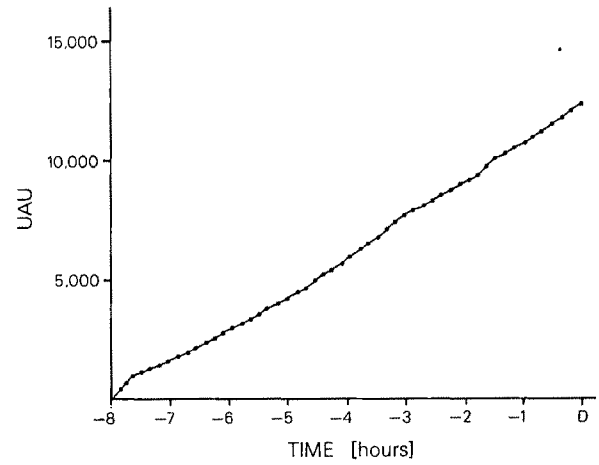


Fig. 2. Cumulative UAU recorded every 10 minutes from 4 cm. to delivery in the patient represented in Fig. 1. The data plotted from Fig. 1 in this fashion show the smooth progressive increase in UAU as labor progresses.

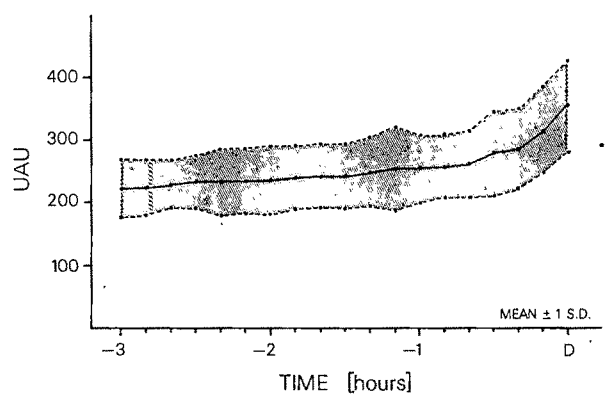


Fig. 3. Mean UAU from 149 patients plotted retrospectively every 10 minutes for 3 hours preceding delivery shows a progressive rise in UA as delivery approaches.

The VCO system has been utilized in several studies evaluating uterine activity,[8, 9] including a study which defined uterine activity in 100 primiparous patients.[10] The primiparous patient required a mean total of 11,536 UAU to progress from 3 cm. to delivery with approximately 20 per cent of this work required for the second stage. This study also demonstrated that the efficiency of uterine contractions increased with advancing labor when work was compared with rate of cervical dilatation, which is in agreement with previous off-line and manual evaluations.

The goal of this study was to define uterine activity in parous patients using an on-line, automated method and compare with previous off-line evaluations. Results from this and other studies should aid in understanding the relationship of uterine activity to progress in labor and define both normal and abnormal labor as seen by an on-line automated method.

Materials and methods

A total of 149 parous patients (P_1 to P_2) who had normal labor curves as described by Friedman[11, 12] were studied in the Perinatal Intensive-Care Unit of Women's Hospital at the Los Angeles County–University of Southern California Medical Center. Patients entering the Perinatal Intensive-Care Unit were more frequently "high-risk" patients than the normal pregnant population. In this study, 109 of 149 patients (74 per cent) had normal, uncomplicated pregnancies. A summary of associated diagnoses of the studied patients is shown in Table I. Only patients having spontaneous vaginal deliveries or elective outlet forceps were included. These patients had routine intrapartum management which at times included analgesics, magnesium sulfate, and paracervical block when clinically indicated. Oxytocin was administered intravenously by an infusion pump when uterine activity was judged to be inadequate by palpation or as reflected in the uterine pressure recording. Local, pudendal, or occasionally epidural blocks were used for delivery. The total study group was divided into two subgroups for comparison: 58 who received oxytocin for either induction or augmentation and the 91 who did not receive oxytocin. The intrauterine pressure was measured with a transcervical, open-ended, fluid-filled catheter connected to a pressure transducer, positioned at the level of the maternal xyphoid. On-line uterine activity measurement was provided in the form of digital print-out in Torr per minutes utilizing a VCO system as previously described. For additional comparison and support, man-

Table I. Obstetric condition

Condition	*Oxytocin group*	*No oxytocin*	*Total*
Normal	44	65	109
Toxemia	4	11	15
Diabetes	4	1	5
Prematurity	2	3	5
Post dates	0	2	2
Rh sensitized	2	0	2
Other	2	9	11
Total	58	91	149

Table II. Length of labor

Hours	*Oxytocin group*	*No oxytocin*	*Total*
0-2	0	2	2
2-4	3	12	15
4-6	10	19	29
6-8	18	31	49
8-10	11	15	26
10-12	6	6	12
12-14	4	2	6
14-16	4	2	6
> 16	2	2	4
Total	58	91	149

ual calculations in Montivideo units were also determined in all cases. All patients also had electronic monitoring and recording of blood pressure, maternal ECG, maternal heart rate, fetal ECG, and fetal heart rate.

Each record was analyzed and the individual data were combined to produce the group profile. Using delivery as an identifiable endpoint, UAU was retrospectively plotted for the preceding labor as it occurred in 10 minute intervals. Shown in Figs. 1 and 2 are examples of plotting nonaccumulative and accumulative UAU, respectively. The data from each patient were reanalyzed in order to evaluate the first and second stages by using complete dilatation and delivery as endpoints.

Next, the mean work per 10 minutes at each centimeter was calculated individually and collectively. This was accomplished by determining the mean UAU for three 10 minute intervals in the 30 minutes surrounding each centimeter change.

The total work expended for each centimeter of dilatation was then calculated for each patient and collectively. When there was a change of 2 cm. between examinations, the total UAU was calculated and divided equally between the 2 cm. Values were not used in this calculation when the change was greater than 2 cm. between examinations. Cervical dilatation of less than 4 cm. was not considered separately in the subgroups because of the small number of parous patients that presented in labor before 4 cm.

Table III. Cervical dilatation at onset of monitoring

Dilatation (cm.)	*Oxytocin group*	*No oxytocin*	*Total*
2	8	0	8
3	8	6	14
4	27	29	56
5	11	26	37
6	2	13	15
7	2	8	10
8	0	5	5
9	0	2	2
10	0	2	2
Total	58	91	149

Table IV. Torr units mean total work*

	Dilatation						
	4-6 cm.		*6-10 cm.*		*10 cm. to del.*		
Group	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Total*
With oxytocin	3,159	53.5	2,132	36.1	616	10.4	5,907
Without oxytocin	1,871	41.6	1,987	44.2	640	14.2	4,498
Combined	2,617	49.4	2,051	38.7	631	11.9	5,299

*The total work expressed in UAU from 4 cm. to delivery is 5,299 UAU with approximately 12 per cent of this activity in the second stage.

Finally, each labor was arbitrarily separated into phases of 4 to 6 cm., 6 to 10 cm., and second stage with amount of work and a per cent of this total calculated for each phase.

Results

The total length of labor ranged from 1.90 to 22 hours. The average length of labor for the total group was 7.35 hours, with the mean time in those receiving oxytocin being 8.45 hours and in those not receiving oxytocin 6.66 hours (Table II). Cervical dilatation at the beginning of the study ranged from 2 to 10 cm. with a mean of 4.7 cm (Table III). A total of 415 vaginal examinations were done in which the cervix had further dilated. In 212 examinations, there had been a 1 cm. progression and in 116 a change of 2 cm. All patients were monitored for at least 30 minutes, with a range of 30 minutes to 8 hours 30 minutes.

Evaluating the total group retrospectively using delivery as an endpoint, there was a progressive increase from 224 UAU per 10 minutes 3 hours prior to delivery to 356 UAU the 10 minutes preceding delivery, as shown in Fig. 3. No significant difference was found in the values when the use of oxytocin was considered.

When the first and second stages were separately

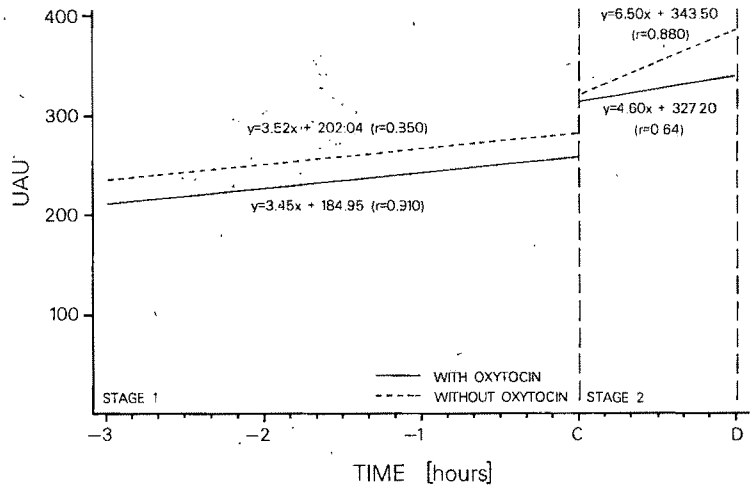


Fig. 4. Regression lines from the data for first and second stages of labor. Solid line = 58 patients receiving oxytocin, broken line = 91 patients not receiving oxytocin. Significant difference exists between the stages of labor but not between the subgroups in the same stage.

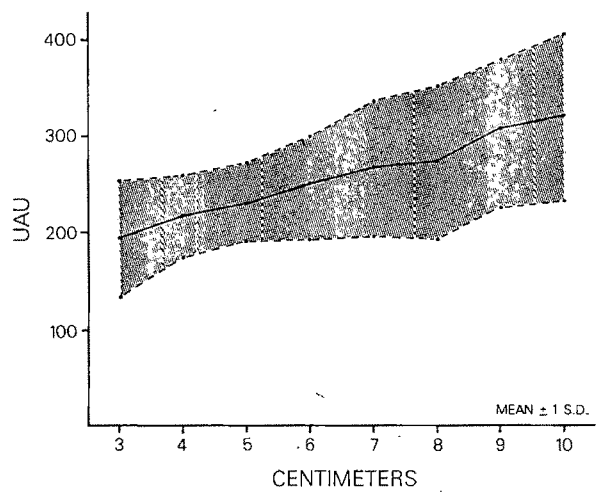


Fig. 5. Mean UAU per 10 minutes at each centimeter of dilatation for 149 patients. The mean UAU increases progressively from 309 at 3 cm. to 545 at 10 cm. dilatation.

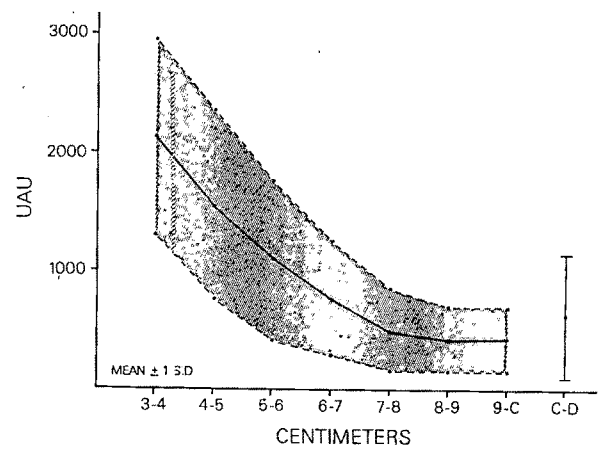


Fig. 6. Mean total UAU expended to progress each centimeter of dilatation in 149 patients showing a progressive increase in the efficiency of the uterine activity as delivery is approached.

analyzed by this method, significantly higher values were encountered in the second stage, as shown in Fig. 4.

The increasing mean work per 10 minutes at each centimeter dilatation is shown in Fig. 5. The standard deviation for each evaluation is wide and the mean values for the oxytocin and nonoxytocin groups are similar, as has been found in other studies.

The total work expended for each centimeter of progress accomplished is plotted in Fig. 6 and shows a progressive decline from 2,132 UAU required to progress from 3 to 4 cm compared to only 428 UAU from 9 to 10 cm. No difference was found between the subgroups after 5 cm. dilatation.

The total uterine activity to achieve delivery is given in Table IV. The per cent of this total required to progress from 4 to 6 cm., 6 to 10 cm., and 10 cm. to delivery is also given, which permits comparison with the reports of Burnhill[13] and Miller[10] and their colleagues and other studies not dividing labor into these exact divisions.

Comment

Hopefully, on-line computer quantitative evaluation of uterine activity will enhance our understanding of the relationship between uterine activity and clinically observed labor. If different phases of labor can be described in precise terms of uterine activity with

abnormal variations defined, clinical applications through the use of on-line electronic monitoring of uterine activity patterns should follow for the practicing obstetrician.

Although individual patients with normal curves have exhibited wide variations when measured both by UAU and MU, certain trends and patterns which have previously been shown off-line can also be observed using the automated on-line approach.

1. The UAU expended per 10 minutes increased steadily as labor advanced, both looking at 10 minute segments retrospectively, or mean 10 minute work at each centimeter.

2. The total UAU expended for each centimeter of dilatation decreased with advancing labor, demonstrating either/or a combination of less resistance or more efficient uterine activity.

3. The total UAU expended by the multiparous patients were 36 per cent less than the primiparous group from 3 cm. to delivery.

4. Within the limits of this study, no difference was observed between patients on the basis of oxytocin.

Certain demonstrated trends have emerged and, hopefully, further work using an automated on-line system will define more precisely abnormal and normal uterine activity patterns, thus enhancing obstetric care.

REFERENCES

1. Crawford, J. W.: Computer monitoring of fetal heart rate and uterine pressure, AM. J. OBSTET. GYNECOL. **121:** 342, 1975.
2. Sokol, R. J., Nussbaum, R. S., and Chik, L.: Computer diagnosis of labor progression, J. Reprod. Med. **11:** 149, 1973.
3. Ledger, W. J.: Monitoring of labor by graphs, Obstet. Gynecol. **34:** 174, 1969.
4. Caldeyro-Barcia, R., Pose, S. V., and Alvarez, H.: Uterine contractability in polyhydramnios and the effects of withdrawal of the excess of amniotic fluid, AM. J. OBSTET. GYNECOL. **73:** 1238, 1957.
5. Samir El Shawi, Gaafar, A. A., and Toppozada, H. K.: A new unit for evaluation of uterine activity, AM. J. OBSTET. GYNECOL. **98:** 900, 1967.
6. Hon, E. H., and Paul, R. H.: Quantitation of uterine activity, Obstet. Gynecol. **42:** 368, 1973.
7. Jilek, J., Hon, E. H., and Yeh, S.: Technique for the measurement of uterine activity, Med. Res. Eng. Sept-Oct.: 45, 1972.
8. Riffel, H. D., Nochimson, D. J., Paul, R. H., and Hon, E. H.: Effects of meperidine and promethazine during labor, Obstet. Gynecol. **42:** 738, 1973.
9. Nochimson, D. J., Riffel, H. D., and Yeh, S. Y.: The effects of ritodrine hydrochloride on uterine activity and the cardiovascular system, AM. J. OBSTET. GYNECOL. **118:** 523, 1974.
10. Miller, F. C., Yeh, S. Y., and Schifrin, B. S.: The quantitation of uterine activity in 100 primiparous patients, AM. J. OBSTET. GYNECOL. **124:** 398, 1976.
11. Friedman, E. A.: The graphic analysis of labor, AM. J. OBSTET. GYNECOL. **68:** 1568, 1954.
12. Friedman, E. A.: Labor: Clinical Evaluation and Management. New York, 1967, Appleton-Century Crofts.
13. Burnhill, M. S., Danezis, J., and Cohen, J.: Uterine contractility during labor studied by intra-amniotic fluid pressure recordings, AM. J. OBSTET. GYNECOL. **83:** 572, 1962.

Maternal deaths in Texas, 1969 to 1973

A report of 501 consecutive maternal deaths from the Texas Medical Association's Committee on Maternal Health

C. E. GIBBS, M.D.
WILLIAM E. LOCKE, M.D.
San Antonio, Texas

The Texas Medical Association's Committee on Maternal Health reports its experience with 501 consecutive maternal deaths. The committee structure and procedures are explained. Demographic and pathologic data are presented and discussed. The defects which allowed complications to proceed to death are analyzed and recommendations are made to reduce the number of these deaths. (AM. J. OBSTET. GYNECOL. 126: 687, 1976.)

THE CAREFUL analysis of deaths surrounding pregnancy has been an effective peer review mechanism for almost 60 years in the United States. The history, functions, and activities of groups organized for this purpose were reviewed in an excellent article by Marmol, Scriggins, and Vollman[1] in 1969. The Texas Medical Association has had such a committee for 40 years. The purpose of this paper is to report the experience of this committee for a recent 5 year period. Demographic, pathologic, and preventability factors will be considered.

Materials and methods

The committee takes its authority from the Texas Medical Association's charge to study all maternal deaths with a view to making recommendations for improving maternal health and is composed of 26 physicians representing various geographic regions and medical disciplines.

The Texas State Department of Health forwards copies of all death certificates of women between ages 14 and 50. Those that are obviously obstetric are identified and the physicians signing all others are asked by mail whether the deceased woman was or had been pregnant. Only about 50 per cent of the deaths can be identified as obstetric from the death certificates alone so that the use of the letters has been mandatory in order to assure good case finding. The appropriate committee member is then informed of the death.

Information concerning all aspects of the case is obtained, recorded, and studied by a county medical society group or by this state-wide committee. When possible, certificates of live births and fetal deaths are obtained from the Department of Health in order to expand the available information. All records are then coded, punch cards are prepared, and the data are entered in the State Department of Health computer. Annual and other reports have been published regularly in recent years.[2-5] The data reported herein were collected and analyzed in the above fashion for the years 1969 to 1973.

Results

Demographic. The committee identified 501 maternal deaths. Table I gives the customary classification and rates as variously defined. The classification is that recommended by the A.M.A.'s Committee on Maternal and Child Care.[6] The pathologic diagnoses will be reported in a later paragraph. Table II lists the data regarding race, marital status, age, and parity. To be especially noted is that 24 per cent of the deaths occurred in individuals 35 and over, although women

From the Department of Obstetrics and Gynecology, The University of Texas Health Science Center at San Antonio.

Presented in part at the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, March, 1975.

Received for publication September 22, 1975.

Revised January 5, 1976.

Accepted February 17, 1976.

Reprint requests: C. E. Gibbs, M.D., Professor, Obstetrics and Gynecology UTHSCSA, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

Table I. Maternal mortality rates, Texas, 1969 to 1973

Live births	1,104,518
Maternal deaths	501
Direct	309
Indirect	95
Unrelated	65
Not classified	32
Rate (direct only)	28.0/100,000 live births
Rate (direct and indirect)	36.6/100,000 live births
Rate (all causes)	45.3/100,000 live births

Table II. Maternal mortality rates and demographic data, Texas, 1969 to 1973

	Per cent of all live births	*Deaths (all causes)*
Race:		
White	58%	39% (196)
Spanish surnamed	27%	32% (161)
Black	15%	27% (134)
Marital status:		
Married	90%	82% (409)
Single	10%	13% (67)
Unrecorded	—	5% (25)
Age:		
< 20	21%	14% (73)
20-34	74%	61% (302)
35-40	4%	18% (89)
> 40	1%	6% (31)
Parity:		
0	40%	24% (122)
1-3	48%	26% (130)
4-6	8%	16% (79)
> 6	4%	10% (50)
Unrecorded	—	24% (120)

Table III. Maternal deaths, Texas, 1969 to 1973: Direct obstetric causes

Hemorrhage:	
Ruptured uterus	28
Postpartum atony	30
Ectopic	20
Abruptio placenta	12
Abortion	4
Placenta previa	3
Other and undetermined	14
Total	111
Other direct:	
Amniotic fluid embolism	21
Anesthesia	16
Other and undetermined	22
Total	59
Toxemia:	
Stroke	25
Heart failure	22
Renal failure	2
Other and undetermined	25
Total	74
Infection:	
Abortion	31
Puerperal sepsis	12
Chorioamnionitis	10
Pyelonephritis	3
Other and undetermined	9
Total	65
Grand total	309

Table IV. Maternal deaths, Texas, 1969 to 1973: Indirect obstetric causes

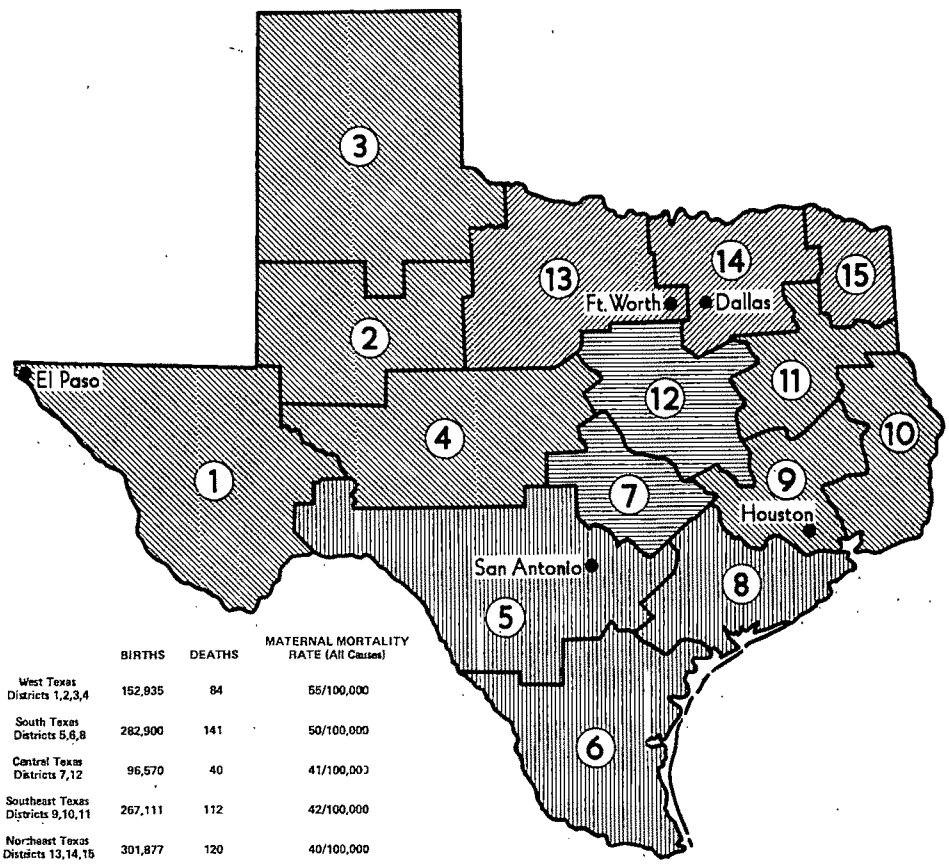
Pulmonary vascular embolism	25
Heart disease	17
Nontoxemia stroke	14
Other and undetermined	39
Total	95

of this age contributed only 5 per cent of the births. High parity was also commonly encountered.

Approximately 7 per cent of the women were residents of farms or ranches but nearly all died within an incorporated city. A total of 108 (22 per cent) indicated that they usually worked for wages; of these, two thirds stated that they were employed at unskilled or semiskilled jobs. Most of the others listed themselves as housewives. Occupations of husbands were available from 218 birth certificates of children born in the pregnancy of death. Of these, 161 (74 per cent) were recorded as unskilled or semiskilled workers and another 2 per cent as unemployed.

Geographically the deaths were distributed throughout the state. The 5 urban counties of Dallas, El Paso, Fort Worth, Houston, and San Antonio recorded 47 per cent of the births and 50 per cent of the deaths with mortality rates from all causes ranging from 33 to 81 per 100,000 live births. The 15 councilor districts exhibited equally wide ranges. Fig. 1 indicates births, deaths, and rates for five regions made up of two or more councilor districts each.

Pathologic. Tables III, IV, and V recorded the deaths by pathologic diagnoses. Autopsy reports were available for only 260 deaths. For the remainder, a clinical diagnosis was assigned for final coding only when the committee was in general agreement. For example, often it was the consensus that the patient died of hemorrhage (or infection, or toxemia) but the precise pathologic process was not clear. Amniotic fluid embolism was allowed only on autopsy evidence. A coagulation defect was usually considered as a secondary manifestation of another disorder so it is not listed separately. It was a factor, however, in perhaps 30 or



	BIRTHS	DEATHS	MATERNAL MORTALITY RATE (All Causes)
West Texas Districts 1,2,3,4	152,935	84	55/100,000
South Texas Districts 5,6,8	282,900	141	50/100,000
Central Texas Districts 7,12	96,570	40	41/100,000
Southeast Texas Districts 9,10,11	267,111	112	42/100,000
Northeast Texas Districts 13,14,15	301,877	120	40/100,000

Fig. 1. Births, deaths, and mortality rates for five geographic regions. Shown also are the 15 TMA councilor districts.

more deaths. Medical records involved in litigation often were not available and of course some hospitals and physicians refused to make their records open to the members of the committee. Thirty-two deaths could not be classified although certainly maternal in time.

Preventability. Preventability was discussed in each case. Many times the available information did not permit a clear judgment. Table VI gives the determination for the direct causes only. Deaths from illegal abortion were generally considered preventable by patient factors, and physician factors were included only if management of the infection or hemorrhage was unsatisfactory. Physician factors alone were identified in about one third of the deaths and, with patient factors, were involved in another 15 per cent. The institution was identified only in association with patient or physician factors.

An attempt was made to determine the quality of the prenatal care but the information is far from complete. It can be affirmed, however, that it was either absent or badly inadequate in 143 cases. Conversely, 182 of the women had quite satisfactory prenatal care.

Table VII gives the status of the pregnancy at the time of death. Fetal death certificates were issued in 96 of the deliveries after 20 weeks. Live birth certificates were available for 263 additional cases and physicians, including 18 D.O.'s, signed all but seven. Granny midwives were identified on the birth certificates of only five, although they may have been involved in others.

Comment

The data on ethnicity, marital status, age, and parity are similar to those of many other large series. Information concerning occupations is available only from birth certificates so that documents of patients who die undelivered or because of abortion and ectopic pregnancy customarily do not provide this information. Also, birth certificates of single patients contain no husband information. However, the information that was available is useful as it demonstrates that large

Table V. Maternal deaths, Texas, 1969 to 1973: Not related

Infection	14
Neoplasia	8
Accident	7
Suicide	6
Drug overdose	2
All others	28
Total	65

Table VI. Maternal deaths, Texas, 1969 to 1973: Preventability—direct causes

	Physician	*Patient*	*Two or More*	*Unavoidable*	*Undetermined*
Hemorrhage	55	11	15	21	9
Infection	14	22	9	15	5
Toxemia	16	19	18	15	6
Other	18	4	2	29	6
Totals	103	56	44	80	26

Table VII. Maternal deaths, Texas, 1969 to 1973: Status of pregnancy at death

Abortions	35
Ectopics	20
Intrauterine (antepartum)	80
Intrauterine (intrapartum)	20
P.P. < 24 hr.	136
P.P. 1-28 days	137
P.P. 29-90 days	24
Unknown	49

numbers of the patients come from low-income groups. The care of medically indigent obstetric patients in Texas is considered to be a local responsibility. City-county hospitals are available in some of the 254 counties and these are by law restricted to serving residents of the county in which they are located. Services for prenatal patients are not present in all counties, much less in all towns. For example, 178 counties do not have local health departments. Thus, delay in obtaining prenatal care occurs at least partly because it is not readily available and would take an inordinate amount of aggressiveness to find it. Likewise, there are many patients who are not likely to request care and who come from cultures in which prenatal care has not been part of a customary life style.[7]

The two regions with the highest mortality rates have much in common. Sixteen of the deaths reported therefrom were nonresidents and this phenomenon was not noted elsewhere in the state. These two regions border on Mexico and many births from Mexican citizens are registered. Spanish-surnamed individuals constitute a large part of the population in these areas and the traditional folk medicine common to many of these persons has not included prenatal care, physician attendance, or hospital delivery. For example, in 1972 the San Antonio yellow pages listed 23 "parteras" (midwives). Until very recently these regions contained no medical schools and few residency training programs. Other problems such as fear, superstition, language barriers, poverty, and the lack of transportation are more difficult to document for an entire region. They have been documented, however, for one county.[7] Much as been made about the great distances and sparse population, and these do constitute problems. However, almost 50 per cent of the deaths in these two large regions occurred in the two urban counties of Bexar (San Antonio) and El Paso. Geographic factors play an important role but those factors are not distance nor low population density. Rather, they are cultural and economic.

Eighty per cent of the deaths were either direct or indirect, a larger precentage than in a series of 551 maternal deaths reported from California some years ago.[8] There can be no question that the problem of maternal death is directly related to the quality of obstetric care. Women died of obstetric hemorrhage, for example, because of failure to diagnose ruptured uterus or disseminated intravascular coagulation. The syndrome of postpartum hemorrhage, death, and an autopsy showing a ruptured uterus as a surprise was all too common. Previous cesarean section and oxytocin were factors in only a very few of these 28 deaths. It seems clear to us that death occurs from ruptured uterus because the classical conditions are not present and therefore the possibility is not considered. Grand multiparas, breech presentation, very large infants, abruptio placentae, and spontaneous tumultuous labor were the usual kinds of conditions with unsuspected ruptured uteri. Treatment errors were related to lack of vigorous approach. Transfusions were frequently too little and too late, often due to failure to perceive the extent of the hemorrhage and only occasionally due to the failure of a small hospital to provide the kind of blood banking required. Ecbolic agents, plasma expanders, prompt hysterectomy, and/or internal hypogastric ligation were often not employed appropriately.

Although pre-eclampsia is a disease of young primigravidas, death associated with toxemia in our patients occurred more commonly in the older age group. In a review of the California experience by Hibbard,[9] the average age of death from toxemia was almost 28 and most of the patients were multiparas.

Toxemia was a frequent cause of death in the over 35 age group. In agreement with the findings of Hibbard, one third of our patients died of cerebral vascular accidents. However, unlike his experience, pulmonary edema/congestive heart failure claimed another third in our series. Most of the toxemia deaths could have been prevented by preventing unwanted pregnancy.

The same statement can be made for infection as almost half of the infection deaths were related to illegal abortion. The Supreme Court decision invalidating the Texas abortion laws was made in the first month of the last year of this report so that the data reflect primarily a period of time in which there was no legal abortion in Texas. A major challenge in management of infection in obstetrics is the detection and treatment of septic shock and, as in hemorrhage, the treatment usually was too little and/or too late. There were several deaths from peritonitis following cesarean section, most of which would have been prevented with prompt surgical treatment.

Reference has been made to the impact of the unwanted pregnancy in maternal death. Illegal abortion, high parity, older reproductive age, and concomitant medical illness all contribute to that large group of women who are pregnant and wish they were not. During these 5 years federally funded opportunities in family planning became increasingly available to medically indigent patients. At the present time, perhaps 55 to 60 per cent of the patients in urban communities and 20 to 25 per cent in the rural are being served by various family planning projects. Safer alternatives to illegal abortion, easier and less expensive methods of permanent sterilization, and readily available contraceptives can be expected to have a very favorable influence on the numbers of maternal deaths.

In assessing preventability, failure to avoid pregnancy was never considered a factor. Preventable factors associated with physician's care were much more often judgmental and informational than technical. For all causes, delay in diagnosis with subsequent delay in treatment was a more common factor than inappropriate treatment. Although it is very difficult to document with figures, it is apparent to the committee that there are Texas physicians caring for pregnant women who would prefer *not* to be doing so. This reluctance, coupled with a complacency of "normal" obstetrics, results in little effort by these individuals to prepare themselves, their patients, and their assistants for obstetric danger. Thus, early signs go unobserved or not investigated until extensive and complex management is required and is often not available.

In a T.M.A. symposium some time ago the question was asked, "Why do pregnant women die?"[10] For Texas from 1969 through 1973 the question can be answered in part as follows: (1) Because the diagnosis of ruptured uterus was not made and/or hemorrhage therefrom was not properly treated. (2) Because postpartum hemorrhage was not anticipated and/or recognized. (3) Because pregnancy was not avoided by women who did not want to become pregnant. (4) Because there was no easy and safe alternative to illegal abortion. (5) Because obstetric infection and particularly septic shock was not managed correctly. (6) Because of delays in receiving prenatal care for reasons both patient-based and societal.

Many things can be done to reduce the maternal mortality rate in Texas. The following four activities would be effective and should be within reach during the next 5 to 10 years. (1) Reduce unwanted pregnancy by more widespread utilization of contraceptives and sterilization. (2) Make available easily accessible ambulatory services for pregnant women, including pregnancy diagnosis, prenatal care, and elective termination. (3) Increase the probability that obstetric care is given by persons interested in giving it. The quality and quantity of such care should be appropriate to patient needs. Various kinds of medical personnel, including certified nurse-midwives, may be utilized in such programs. (4) Develop and integrate consultation and referral services into an acceptable program of continuing education.

We wish to express our sincere appreciation to Mr. Don Carroll and Mr. Carl Welge of the Texas State Department of Health for their unfailing courtesy and excellent assistance in case finding and data processing. We also are greatly indebted to Mrs. Barbara Duke, the diligent and gracious staff aide to the Committee over the past 8 years.

REFERENCES

1. Marmol, J G, Scriggins, A. L., and Vollman, R. F.: History of the maternal mortality study committees in the United States. After office hours, Obstet. Gynecol. **34:** 123, 1969.
2. Gibbs, C. E.: Committee reports on Texas' maternal deaths, Texas Med. **67:** 37, 1971.
3. Gibbs, C. E.: Texas' maternal deaths, Texas Med. **69:** 137, 1973.
4. Gibbs, C. E.: Committee reports on maternal deaths, Texas Med. **70:** 20, 1974.
5. Gibbs, C. E.: Maternal deaths due to stroke, Am. J. Obstet. Gynecol. **119:** 69, 1974.
6. Wright, W. A., and Morgan, H. S.: A guide for maternal

A new, more sensitive tube test for pregnancy evaluated with a selected hospital population

LOUISE LANG, M.T.(A.S.C.P.)
ALICE M. REISS, PH.D.
With the technical assistance of
LINDA SMITH
MARCIA KERBER
Hamilton, Ohio, and Raritan, New Jersey

A new tube test for pregnancy, having a sensitivity of 0.5 I.U. of human chorionic gonadotropin per milliliter, was evaluated, along with two other commercially available kits, in a hospital patient population. Of 586 patients in the study, 302 were in nonobstetric services and many were acutely ill. Approximately one fourth of the women were age 40 or older. The medical records of 66 per cent of the patients were retrieved to obtain information on the drugs administered prior to pregnancy testing. A small number of problems did occur in the pregnancy test procedures. Inconclusive results were recorded for both pregnant and nonpregnant patients and could not be correlated with disease states and/or medications. The importance of a reagent control for tube test procedures is discussed. (AM. J. OBSTET. GYNECOL. 126: 693, 1976.)

THE DEVELOPMENT OF simple immunologic tests for pregnancy based on the detection of human chorionic gonadotropin (HCG) has provided a practical means by which women in the childbearing age can be screened quickly and reliably. For a period of two years, our laboratory has routinely used the Gravindex* slide test, the UCG-test,† and a tube test under development that is now commercially available as the Gravindex* tube test. The new tube test procedure has a sensitivity of 0.5 I.U. of HCG per milliliter and does not require dilution of the urine specimen prior to testing. A reagent control tube is provided for each specimen to establish that there are no urinary constituents causing interference in the reagent system.

From Mercy Hospital, Hamilton, and Ortho Research Institute of Medical Sciences, Ortho Diagnostics, Inc., Raritan.

Received for publication February 20, 1976.

Accepted April 9, 1976.

Reprint requests: Louise Lang, M.T.(A.S.C.P.), Mercy Hospital, Hamilton, Ohio 45011.

**Ortho Diagnostics, Inc., Raritan, New Jersey 08869.*

†Wampole Lab., Div. of Denver Chem. Mfg. Co., 35 Commerce Rd., Stamford, Connecticut 06904.

Material and methods

A total of 1,461 urine specimens were tested in parallel with the three test kits mentioned above. After study of the first 875 specimens, a change in the buffer system of the Gravindex tube test was made to reduce the number of inconclusive results which had necessitated repeat testing. The findings with the use of the modified buffer system on 586 patients are presented in this paper.

The result of each test was recorded, together with appropriate patient identification, age, and clinical diagnosis. Each specimen was tested for specific gravity and protein content. Known nonpregnant patients were selected for the study with the expressed purpose of seeking unsuspected urinary constituents that could interfere with pregnancy test procedures. The patients included women of menopausal age, 40 to 55 years old, and postmenopausal age, over 55 years old, as well as patients with acute myocardial infarct, hepatitis, pancreatitis, acute cholecystitis, carcinoma, diabetes, urinary tract infection, and drug overdose.

To study the possible effects of drugs on test accuracy, the hospital charts of 387 of the 586 patients were retrieved after the test results had been tabulated. Notation was made of each drug and the dose level

Table I. Results obtained on 586 patients

Patient category	No. tested	Test results		
		Positive (%)	Negative (%)	Inconclusive (%)
Pregnant				
Gravindex tube test	231	224 (97.0)	0 (0)	7 (3.0)
UCG-test	231	220 (95.2)	7 (3.0)	4 (1.7)
Gravindex slide test	231	218 (94.3)	13 (5.6)	0 (0)
Abnormal pregnancies				
Gravindex tube test	53	39 (73.6)	12 (22.6)	2 (3.8)
UCG-test	53	27 (50.9)	22 (41.5)	4 (7.5)
Gravindex slide test	53	25 (47.2)	28 (52.8)	0 (0)
Nonpregnant				
Gravindex tube test	302	4* (1.3)	291 (96.4)	7 (2.3)
UCG-test	301	4* (1.3)	295 (98.0)	2 (0.7)
Gravindex slide test	302	3* (1.0)	299 (99.0)	0 (0)

*One patient, age 68, all tests positive, 3+ albumin, arterial sclerotic heart disease (ASHD); one patient, age 19, all tests positive, 3+ albumin, acute cystitis (an unrecognized abortion cannot be ruled out with certainty); one patient, age 45, tube tests positive, 1+ albumin, pyelonephritis; one patient, age 61, tube tests positive, 2+ albumin, terminal hepatic coma; one patient, age 23, slide test positive, 1+ albumin, uterine bleeding.

administered in the 48 hour period prior to performance of the pregnancy tests.

The Gravindex tube test was used according to the directions in the clinical research protocol which corresponds to the direction circular in the commercially available kit. The other two kits were used according to the manufacturers' directions.

Results

The patients studied and test results are shown in Table I. The 231 patients who were categorized as pregnant include those in all trimesters of pregnancy as well as a small number of postpartum women. No false negative reactions were recorded with the Gravindex tube test as compared to 7 false negative results with the UCG-test and 13 with the Gravindex slide test. The seven inconclusive results with the Gravindex tube test and the four with the UCG-test required repeat testing of the same specimen or testing of a new specimen.

The 53 abnormal pregnancies include abortions (threatened, incomplete, and missed) and ectopic pregnancies. The increased sensitivity of the Gravindex tube test is readily apparent in this group with well-recognized low levels of HCG. Twenty-eight of the 53 patients had concentrations of HCG less than 3.5 I.U. per milliliter as determined by the Gravindex slide test. Twenty-two patients had levels less than 3.0 I.U. per milliliter as determined by the UCG-test, and 12 patients, with abnormal pregnancies not detected by the Gravindex tube test, had concentrations of less than 0.5 I.U. of HCG per milliliter of urine.

The 302 nonpregnant female patients included many that were acutely ill. The rationale for studying these patients was that the shortcomings of a pregnancy test would be recognized much more quickly in a hospital patient population. About one fourth of this group consisted of women in the menopausal and postmenopausal age groups. The clinical diagnoses in the cases of the four hospitalized patients yielding false positive pregnancy tests are given at the bottom of Table I. The 68-year-old and 61-year-old patients were moribund at the time of testing. The 19-year-old patient with a diagnosis of cystitis had positive results with all three test procedures. Although clinical follow-up showed the patient to be nonpregnant, an unrecognized abortion cannot be ruled out with certainty. The 45-year-old woman with a diagnosis of pyelonephritis had a false positive result in both tube test procedures but a negative result with the slide test method.

Numerous other patients with cystitis and pyelonephritis were tested with accurate results. It is possible that certain bacteria or bacterial or viral products, when present in sufficient quantities, adsorb to the surface of the carrier particles and prevent antigen-antibody interaction by steric interference. This can be demonstrated indirectly for some of these problems by washing the HCG-carrier particles after the false positive reaction has occurred. The addition of these washed HCG-carrier particles to reagent anti-HCG and known problem-free nonpregnant urine will show that the HCG-carrier particles still cannot be agglutinated. While such manipulations are not always successful, the results do indicate that false positive reactions should not invariably be interpreted as resulting from pituitary luteinizing hormone (LH).

It can be seen that a number of the urine specimens

in each category were reported as inconclusive for the tube test procedures. In the absence of the respective reagent controls, there would have been no warning for the laboratory of an inherent problem with the urine specimen. It can also be seen that the interfering factors did not affect the Gravindex slide test reactions.

A number of cases of drug overdose established by thin-layer and gas chromatography were included in the study. Urine samples containing hard drugs and methadone were also included. None of these cases showed interference in the respective test systems. These patients are not included in the 387 whose charts were retrieved for the purpose of reviewing the number and type of drugs administered in the 48 hour interval prior to performance of the pregnancy tests.

A summary of the number of patients receiving medications within a major category was compiled and is shown in Table II. The number of drugs prescribed was much greater than expected. Medications given averaged three per patient, with a range from zero (patients tested upon admission) to 27 for one patient and 26 for another. Neither of these patients gave false pregnancy test results. Some patients were receiving seven to 10 drugs simultaneously. It is not surprising that a recent publication[1] suggested routine screening of female subjects admitted to the hospital to identify pregnant patients prior to prescription of drugs and performance of certain diagnostic procedures.

Table II. Drug study on 387 patients: Medication received during pregnancy testing

Patients (No.)	*Major drug category*
168	Barbiturates
162	Tranquilizers, sedatives
103	Narcotics
87	Hormones, enzymes
87	Analgesics, salicylates
80	Antihistamines
72	Antibiotics
39	Antipruritics
34	Laxatives
30	Oxytocic compounds
17	Vitamins
9	Diuretics
9	Anticoagulants
100	Defined miscellaneous*
77	Undefined miscellaneous†

*For instance, 27 of 100 received antineoplastic agents.
†For instance, 14 of 77 received gall bladder medication.

Comment

Several significant findings emerged from this study.

The increased sensitivity of the Gravindex tube test (0.5 I.U. of HCG per milliliter) did not pose problems that could be ascribed to the increased levels of LH known to be present in women of menopausal and postmenopausal ages. This finding is consistent with that previously reported by Albert[2] who showed that the urine of a castrated woman known to excrete an extremely high level of LH was not able to neutralize anti-HCG in the Gravindex slide test even after a tenfold concentration of urine by a tannic acid procedure. In fact, the level of LH after concentration with the tannic acid procedure was only 5 per cent of that required for a false positive result. Cross-reactivity between anti-HCG and LH is well established.[3–5] However, the conclusion that false positive results obtained when testing urine samples of older women are attributable to LH is not always justified.

The problem of interfering substances being responsible for inconclusive results with the UCG-test was previously reported by Lang.[6] In a recent publication by Garment and associates,[1] inconclusive results were shown for the Dri-Dot* slide test as well as for the Accusphere* tube test procedure.

In our experience, the factors causing problems in the interpretation of pregnancy tests (with special reference to tube tests for pregnancy), although increased in older women, nevertheless may occur at any age and do not appear to be hormone related. Some interfering factors result in the agglutination (to a variable degree) of the sheep red cell–HCG antigen in the absence of anti-HCG. The problem can be discerned only when a reagent control tube, with the identical buffer system present in the test reagent, is an integral part of the testing procedure. In the absence of a reagent control, the tube test result would be recorded as negative for pregnancy. These interfering factors are just as frequent in apparently healthy pregnant women as in nonpregnant women. Often, the interfering factors are sufficiently labile as to disappear in the time interval required to repeat the test. When this does not occur, a repeat specimen usually gives clear-cut results. The unstable and elusive nature of the interfering substances has made characterization extremely difficult, but the substances are not related to pH, specific gravity, or protein concentration in the urine. The possible interference of drugs or drug metabolites cannot be ruled out with absolute certainty in view of the almost infinite number of combinations and dose levels, but the data do indicate that medications need not be a major concern with regard to the reagents studied.

*Organon, Inc., 375 Mt. Pleasant Ave., West Orange, New Jersey 07052.

REFERENCES

1. Garment, M. B., Ladinsky, J. L., Gottlieb, L. I., and Larson, F. C.: A study on the advisability of routine hospital pregnancy testing. J. Lab. Clin. Med. **84:** 920, 1974.
2. Albert, A.: Procedure for concentrating urine for use with an immunologic test for pregnancy, Mayo Clin. Proc. **45:** 114, 1970.
3. Paul, W. E., and Ross, G. T.: Immunologic cross-reaction between human chorionic gonadotropin and human pituitary gonadotropin, Endocrinology **75:** 352, 1964.
4. Reiss, A. M., Singher, H. O., Hawk, J. B., et al.: Immunologic cross-reaction between luteinizing hormone and antisera to human chorionic gonadotropin, Int. Arch. Allergy **30:** 561, 1966.
5. Wide, L.: An immunological method for the assay of human chorionic gonadotropin, Acta Endocrinol. **41:** 49, 1962. (Suppl. 70.)
6. Lang, L.: Interfering substances of menopausal urine for red cells coated with human chorionic gonadotropic hormone, Am. J. Med. Technol. **31:** 373, 1965.

Screening for detecting twin pregnancy

MADIS MÄGISTE, M.D.
HENNING VON SCHENCK, M.D.
NILS-OTTO SJÖBERG, M.D.
JAN I. THORELL, M.D.
ANDERS ÅBERG, M.D.
Lund, Sweden

Estimation of HPL during the twenty-ninth to the thirtieth week of pregnancy is a simple and safe method for detecting twins. Nine out of 10 pregnant women have a value below 5.0 μg per milliliter, which excludes the suspicion of twins. In the remaining women with higher values the diagnosis can be confirmed or excluded by ultrasound or x-ray. (AM. J. OBSTET. GYNECOL. 126: 697, 1976.)

PREGNANCY involving one child is—or should be—natural and safe as long as certain precautions and antenatal care are observed. Twin pregnancy has a much higher perinatal mortality rate—about 10 per cent.[1, 2] Moreover, the danger of morbidity is far greater for both mother and children.[2] The main causes of bad prognosis in twin pregnancy are the increased risk of pre-eclampsia, polyhydramnios, anemia, and delivery complications and the increased frequency of premature delivery.[1, 3, 4] To avoid premature labor, patients have frequently been controlled throughout the pregnancy or hospitalized.[5] The prognosis for twin pregnancy is considered improved by early diagnosis. Unfortunately, it is rare that the presence of twins is confirmed before the twenty-eighth pregnancy week[6]; about 50 per cent of all twin pregnancies are discovered only at delivery.[7] Therefore a simple screening to provide an exact diagnosis as early as possible before the mentioned complications can arise would be of the utmost value.

Human placental lactogen (HPL), also called human chorionic somatomammotropin (HCS), has long been used in obstetric practice as an indicator of the placental function.[8] Publications recording isolated instances of twin pregnancies have reported that the HPL value for these patients has been high throughout.[8, 9] An estimate of the HPL might therefore be a simple method for the early diagnosis of twin pregnancy.

Since May, 1973, a venous blood sample has been taken from all pregnant women in the university town of Lund and its environs during weeks 29 to 30 of pregnancy. The midwife takes about 5 ml. of venous blood in an EDTA tube. After centrifugation, 1 ml. of the plasma is sent to the laboratory, where the HPL is estimated by a radioimmunoassay performed according to the method described by Letchworth and associates.[10] HPL from Nutrional Biochemical Corporation has been used as a standard. The same preparation is used for radioiodination. EDTA-plasma (100 μl) is mixed with 200 μl of ^{125}I-HPL in a buffer, and 200 μl of diluted antiserum are then added. After 1 hour's incubation at room temperature, HPL is separated in its free and its bound forms with concentrated ethanol. The radioactivity of the precipitate is counted in a gamma scintillation counter. The result is read on a standard curve.

HPL increases continuously during pregnancy. In weeks 29 to 30 of pregnancy (simplex pregnancies) the HPL value of 5.0 μg per milliliter is in the upper part of the reference range. Pregnant women with HPL values of 5.0 μg per milliliter or more were investigated by ultrasound to confirm or exclude the diagnosis of twin pregnancy. Up to February, 1975, HPL was estimated in 1,766 pregnant women during weeks 29 to 30 of pregnancy (Table I). In 236 women (13.4 per cent), the HPL value was 5.0 μg per milliliter or more. Ultrasound confirmed the diagnosis of twin pregnancy in 32 (13.6 per cent) of the 236 patients. No women

From the Department of Obstetrics and Gynecology, Lund, and the Department of Isotop laboratory, Malmö, University of Lund.

Received for publication January 21, 1976.

Accepted March 9, 1976.

Reprint requests: Dr. Nils-Otto Sjöberg, Department of Obstetrics and Gynecology, Lund University Hospital, S-221 85 Lund, Sweden.

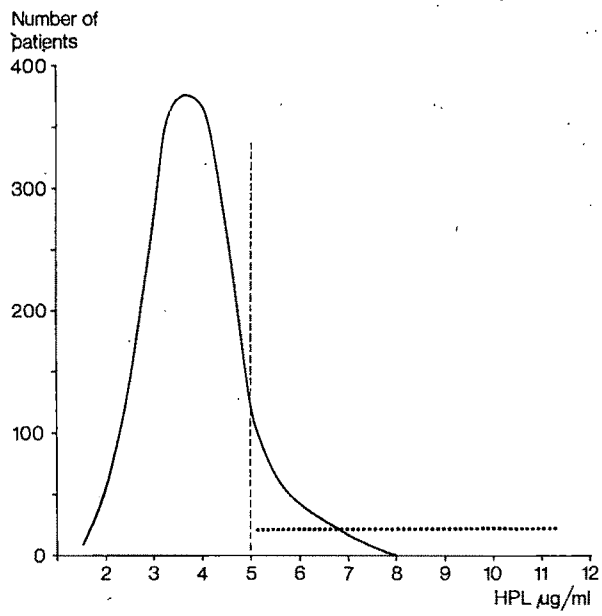


Fig. 1. Range of HPL-values during the twenty-ninth to the thirtieth week of pregnancy: the continuous line denotes simplex pregnancies; the dotted line, multibirth pregnancies. The dashed vertical line signifies the screen limit of ultrasound examination.

with HPL values less than 5.0 µg per milliliter were delivered of twins.

In simplex pregnancies, the mean value ±2 S.D. for HPL during pregnancy weeks 29 to 30 was 3.9 ± 2.0 (Fig. 1). The value for the multibirth gravidas was 7.3 ± 2.6. The lowest value registered among the multibirth gravidas was 5.1 µg per milliliter. The highest HPL value was 11.3; this was in a woman with triplets.

Table I. Number of pregnant women in the twenty-ninth to the thirtieth week of pregnancy with HPL values less than 5.0 µg per milliliter and those with value of 5.0 µg per milliliter or more

	HPL (µg/ml.)	*No. of pregnant women*
Not examined by ultrasound	<5	1,530 (0)*
Examined by ultrasound	≥5	236 (32)
Total		1,766 (32)

*Numbers of multibirth gravidas within parentheses.

To carry out an x-ray or ultrasound examination of all pregnant women is time consuming and expensive, and not every clinic has the necessary facilities. However, a preliminary screening with estimate of HPL during weeks 29 to 30 of pregnancy is a simple, cheap, and safe method for detecting twin pregnancies. The study has shown that, where values lie below 5.0 µg per milliliter of serum it is safe to exclude the suspicion of twin pregnancy. Where the HPL value is 5.0 µg per milliliter or more, x-ray or ultrasound can be used to confirm or exclude the twin pregnancy diagnosis. This means that only about 10 per cent of all pregnant women must undergo one or other of these examinations.

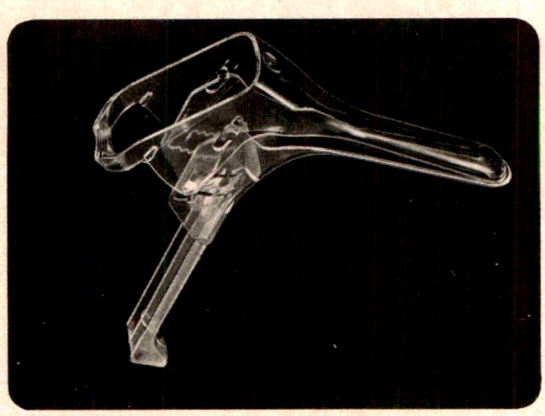
This simple screening promises an improvement in the early diagnosis of twin pregnancies. This can be expected to reduce the high perinatal mortality rate in twins.

REFERENCES

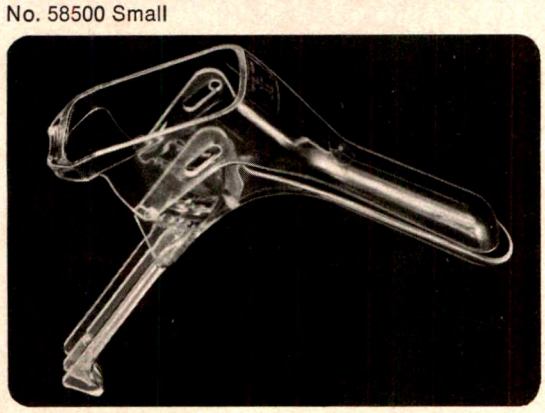
1. Brown, E. J., and Dixon, H. G.: Twin pregnancy, J. Obstet. Gynaecol. Br. Emp. **70:** 251, 1963.
2. Powers, W.: Twin pregnancy; complications and treatment, Obstet. Gynecol. **42:** 795, 1973.
3. Farrell, A. G. W.: Twin pregnancy: A study of 1,000 cases, S. Afr. J. Obstet. Gynaecol. **2:** 35, 1964.
4. Robertson, J. G.: Twin pregnancy: Morbidity and mortality, Obstet. Gynecol. **23:** 330, 1964.
5. Barter, R. H., Hsu, J., Erkenbeck, R. V., and Pugsley, L. Q.: The prevention of prematurity in multiple pregnancy, Am. J. Obstet. Gynecol. **91:** 787, 1965.
6. Minogue, M.: A review of twin pregnancies, National Maternity Hospital, (1967-1971), J. Irish Med. Assoc. **67:** 181, 1974.
7. Ahlström, K.: Prematurprofylax vid tvillinggraviditet, Läkartidningen **71:** 3089, 1974.
8. Josimovich, J. B.: Placental lactogenic hormone, *in* Fuchs, F., and Klopper, A., editors: Endocrinology of pregnancy, New York, 1971, Harper & Row, p. 184.
9. Genazzani, A. R., Cocola, F., Neri, P., and Fioretti, P.: Human chorionic somatomammotropin (HCS) levels in normal and pathological pregnancies and their correlation with the placental function, Acta. Endocrinol. **71:** Suppl. 167, 1972.
10. Letchworth, A. T., Boardman, R. J., Bristow, Ch., Landow, J., and Chord, T.: A Rapid semi-automated method for the measurement of human chorionic somatomammotrophin. The normal range in the third trimester and its relation to fetal weight, J. Obstet. Gynaecol. Br. Emp. **78:** 542, 1971.



PRE-LUBRICATED disposable vaginal specula...now in two sizes.



No. 58500 Small



No. 58501 Regular

Just wet the new Welch Allyn KleenSpec® Pre-Lubricated Disposable Vaginal Specula with water—and they're ready for use!

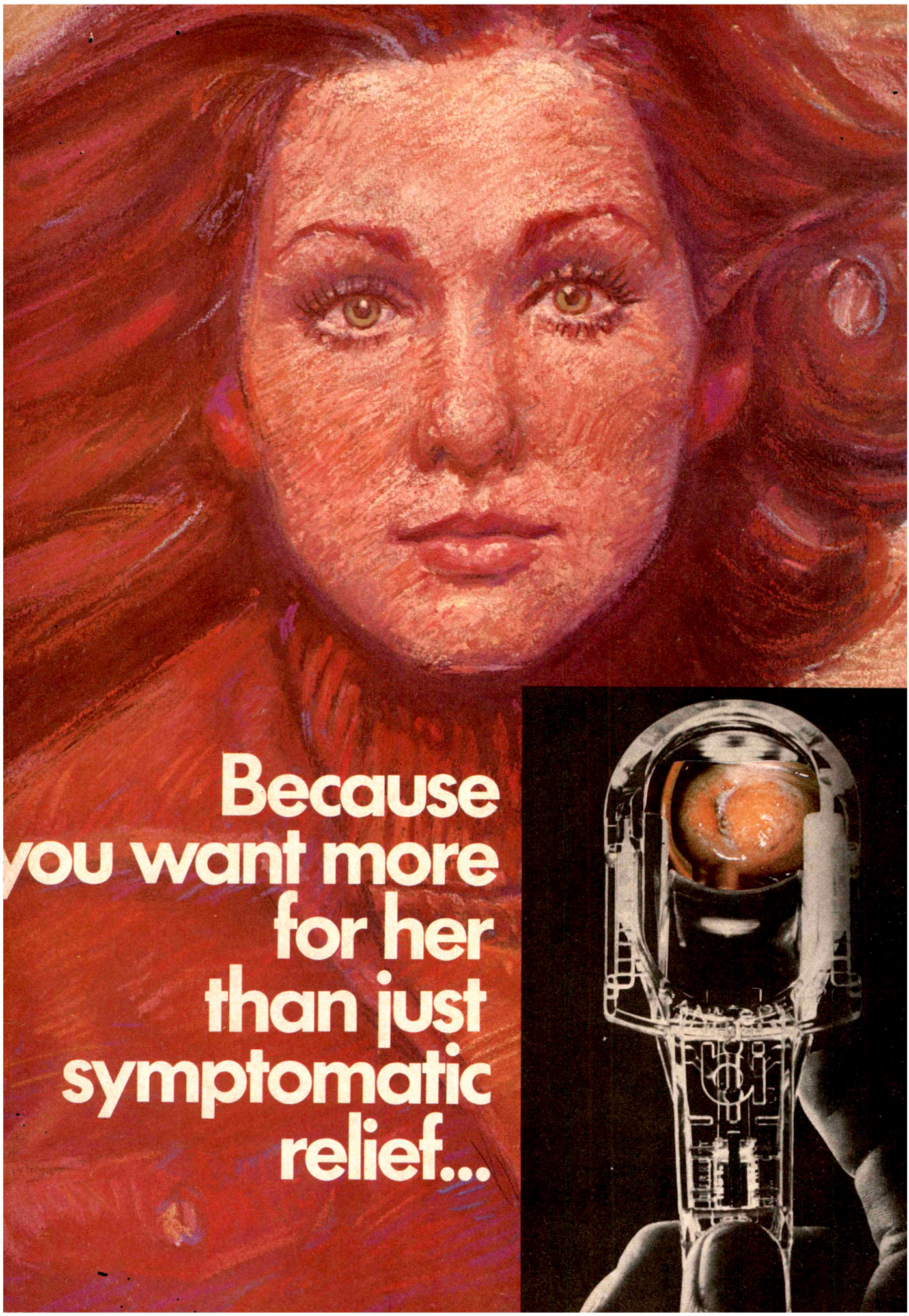
Check these advantages:

- ☐ Compatible with Pap Smear procedures
- ☐ Easier insertion—minimizes trauma
- ☐ Speeds examinations—saves time
- ☐ No cleanup as with ordinary lubricants
- ☐ New small size specula have same advantages as the regular size
- ☐ Individually packaged—assures cleanliness and prevents cross-contamination
- ☐ One-hand operation—elevation plus angulation
- ☐ Built-in mucus barrier
- ☐ Optional fiber optic illuminator No. 78500

Contact your Authorized Welch Allyn Distributor TODAY

WELCH ALLYN

WELCH ALLYN, INC. Skaneateles Falls, N.Y. 13153 U.S.A


Because
you want more
for her
than just
symptomatic
relief...

Sultrin
TRADEMARK

Triple Sulfa Cream/Vaginal Tablets

effective against and specific for H. vaginalis

The cause of over 90% of "nonspecific" vaginitis†

effective

based on review by the National Academy of Sciences/National Research Counsel, Sultrin was rated as "effective" against *H. vaginalis*.

prompt symptomatic relief

often within a few days, patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

versatile adjunct in other vaginitides

Sultrin is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

convenient choice of dosage forms

Sultrin comes as a soothing, non-staining and esthetically pleasing cream or convenient vaginal tablets.

Composition: Each SULTRIN Tablet contains sulfathiazole 172.5 mg, sulfacetamide 143.75 mg, and sulfabenzamide 184.0 mg. SULTRIN Triple Sulfa Cream contains sulfathiazole 3.42%, sulfacetamide 2.86%, sulfabenzamide 3.7% and urea 0.64%.
Indications: SULTRIN Tablets and Cream are indicated for treatment of *Haemophilus vaginalis* vaginitis. They may also be used as a deodorant for saprophytic infection following radiation therapy.
Contraindications: Sulfonamide sensitivity and kidney disease.
Dosage: SULTRIN Tablets: One tablet intravaginally before retiring and again in the morning for ten days. This course may be repeated if necessary. SULTRIN Cream: One applicatorful intravaginally twice daily for 4 to 6 days. The dosage may then be reduced one-half to one-quarter.
Supplied: SULTRIN Tablets are available in packages of 20 foil-wrapped tablets with vaginal applicator. SULTRIN Cream is available in 2.75 oz. (78 g) tubes with the ORTHO* Measured-Dose Applicator. OJ 10-6 *TRADEMARK

†Gardner, H.L. and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

MASSON Publishing USA, Inc.

INTENSIVE CARE IN THE NEWBORN

Edited by:
Leo Stern, M.D., Brown University
Bent Friis-Hansen, M.D., University of Copenhagen
Poul Kildeberg, M.D., University of Odense

A comprehensive review of the most current research and technical developments in neonatal intensive care of the past decade, by 75 internationally recognized leaders.

With a foreword by Norman Kretchmer, M.D., Director, National Institutes of Child Health and Human Development.

A necessary addition to the working library of every neonatal health professional.

Available from:
MASSON PUBLISHING USA, INC.
S.M.P.F. Corp.
14 East 60 Street • New York, New York 10022

and at your medical book store.

1976, 296 pp., 127 illus., hardcover,
ISBN 0-89352-000-4 **$29.50**

UTAH

Chairperson, Department of Obstetrics and Gynecology, the University of Utah College of Medicine.

Applications are invited for the position of chairperson of Obstetrics and Gynecology in the College of Medicine at the University of Utah. The University is an equal opportunity employer.

Replies should be directed to: Lowell A. Glasgow, M.D., Chairman, Obstetrics and Gynecology Search Committee, c/o Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, Utah 84132.

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION (Required by 39 U.S.C. 3685). 1. Title of Publication: AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. 2. Date of filing: October 1, 1976. 3. Frequency of issue: Semi-Monthly. 3A. No. of issues published annually: 24. 3B. Annual subscription price: $27.00. 4. Location of known office of publication: 11830 Westline Industrial Drive, St. Louis, Missouri 63141. 5. Location of the headquarters or general business offices of the publishers: Same as 4. 6. Names and complete addresses of publisher, editor, and managing editor: Publisher—The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141; Editor—John I. Brewer, M.D., 303 East Superior Street, Chicago, Illinois 60611; Managing editor—None. 7. Owner: The C. V. Mosby Company, a corporation, owner of publication, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. All of the stock of The C. V. Mosby Company is owned by Times Mirror Company, a corporation, Times Mirror Square, Los Angeles, California 90053. 8. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: None. 9. Not applicable to The C. V. Mosby Company.

10. Extent and nature of circulation	*Average no. copies each issue during preceding 12 months*	*Actual number of copies of single issue published nearest to filing date*
A. Total no. copies printed *(net press run)*	20,492	20,679
B. Paid circulation		
1. Sales through dealers and carriers, street vendors and counter sales	None	None
2. Mail subscriptions	19,370	18,990
C. Total paid circulation	19,370	18,990
D. Free distribution by mail, carrier, or other means, samples, complimentary, and other free copies	692	559
E. Total distribution *(Sum of C and D)*	20,062	19,549
F. Copies not distributed		
1. Office use, left over, unaccounted, spoiled after printing	430	1,130
2. Returns from news agents	None	None
G. Total *(Sum of E, F1 and 2—should equal net press run shown in A)*	20,492	20,679

11. I certify that the statements made by me above are correct and complete.

A. Jerome Freeland, *Journal Publisher*

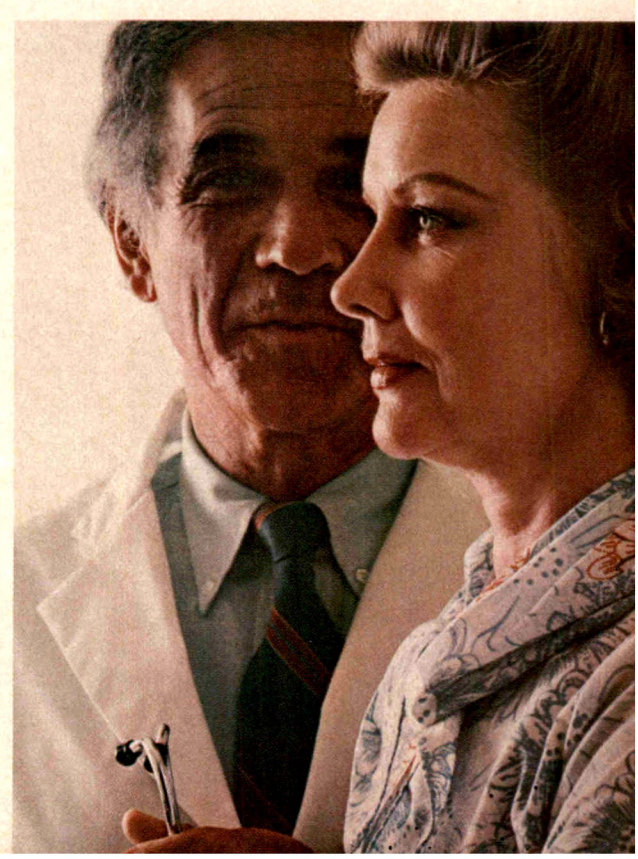
12. In accordance with the provisions of this statute, I hereby request permission to mail the publication named in Item 1 at the phased postage rates presently authorized by 39 U.S.C. 3626.

A. Jerome Freeland, *Journal Publisher*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
IN THE MENOPAUSE TODAY

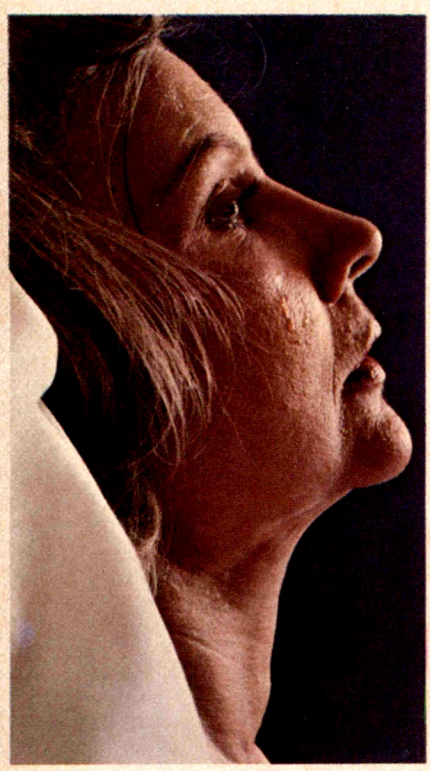
"The height of professional integrity is to prescribe estrogen when needed and indicated, and to withhold it if there is no indication or when a contraindication to its use exists."

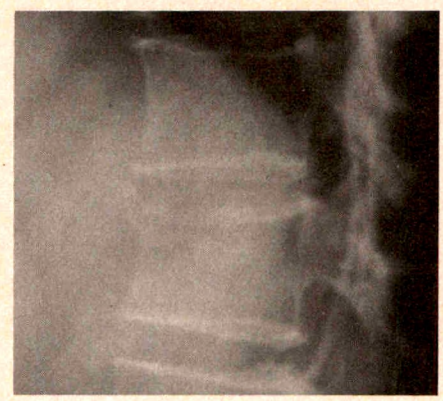
—Barber, H.R.K.:
Editorial, in The Female Patient
1:7 (Mar.) 1976.



Manifestations of estrogen deficiency...

Vasomotor Instability
commonly appearing in the menopause as hot flushes, sweats, palpitations, numbness, and tingling. Hot flushes, a classic symptom of estrogen deficiency, are a clear-cut indication for treatment. The therapeutic goal is well-defined: "...to minimize the intensity of the duration of distressing symptoms as well as to tide the patient over the period of physiologic adjustment. The symptoms vanish in almost all instances if the estrogenic therapy is adequate and well-planned."[1]





Postmenopausal Osteoporosis*
is often related to estrogen deficiency. Effects may not be apparent until a decade or more after the natural menopause, but may be evident in as little as three years after surgical menopause. With the advent of new technics for the accurate measurement of bone density, it has been possible to demonstrate that decrease in mass is related to loss of ovarian function, not age.[2] This has been confirmed by a retrospective study[3] of hysterectomized women with and without oophorectomy.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

Atrophic Vaginitis
often with involvement of related genitourinary structures, is frequently associated with estrogen deficiency. The gradual atrophic changes render vulvovaginal and urethral tissues more susceptible to trauma, inflammation, and secondary infection which may lead to pruritus and pain, dyspareunia, dysuria and incontinence. Replacement therapy helps to restore genitourinary tissue to a healthier, more normal state. The uncomfortable symptoms are often promptly controlled by estrogen therapy.



In addition, surgical menopause presents the signs of abrupt estrogen deficiency in their most acute fashion: not only vasomotor flushes and sweats, but other common symptoms of the menopausal syndrome, as well. These symptoms are usually rapidly relieved by adequate estrogen therapy.

1. Israel, S.L.: Diagnosis and Treatment of Menstrual Disorders and Sterility, ed. 5, New York, Harper & Row, 1967, p. 398.
2. Meema, S., *et al.*: Arch. Intern. Med. *135*:1436 (Nov.) 1975.
3. Aitken, J.M., *et al.*: Br. Med. J. 2:325 (May 12) 1973.

Management of estrogen deficiency...

Management of estrogen deficiency symptoms includes the appropriate use of estrogen replacement therapy, and requires three basic principles of good medical management: the proper patient...the proper dosage...and the proper precautions.

The Proper Patient...
is, of course, the woman who presents significant symptomatology of estrogen deficiency in the absence of any contraindications. Pretreatment assessment of the patient should include a complete physical examination and careful history-taking to determine personal or familial incidence of carcinoma, hypertension, thromboembolic disorders, or undiagnosed abnormal genital bleeding. Repeatedly, estrogens have been shown to be of benefit in relieving the manifestations of estrogen deficiency. Although the evaluation of estrogen deficiency may be assisted by vaginal cytology, the principal criterion for treatment is still the degree of symptomatology.

The Proper Dosage...
should be the lowest dosage that relieves the patient's symptoms, as determined by empirical trial. With PREMARIN, the usual starting dosage for the common symptoms of the menopause is 1.25 mg per day for three weeks, followed by a one-week rest period. Following an adequate trial period, this dosage may be titrated upward or downward depending upon severity of symptoms and individual patient response. In prophylactic use for the prevention of osteoporosis,* PREMARIN, in conjunction with other recognized measures, may be effective in a dose of 0.625 mg per day, administered cyclically. In advanced osteoporosis, PREMARIN, 1.25 mg per day, is usually the recommended dosage to retard progression and reduce the incidence of further fractures.

The Proper Precautions...
should include cyclic administration—three weeks on, one week off, to avoid prolonged stimulation of the endometrium and breasts; at least annual checkups, including breast and pelvic examinations; and the thorough and prompt investigation of any unexplained vaginal bleeding and/or breast changes. In addition, the need for therapy should be reassessed on an annual basis to determine if estrogen replacement therapy is still required for symptomatic relief.

These precautions are representative of the prudent approach to estrogen replacement therapy.

PREMARIN continues to be highly efficacious in relieving and preventing the physical and physiological consequences of estrogen deficiency. When indicated, and utilizing the appropriate precautions, patients can experience the therapeutic benefits of estrogen replacement therapy today.

Three studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. For further information see "Warnings" in prescribing information.



ESTROGEN REPLACEMENT THERAPY

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

Estrogens obtained exclusively from natural sources

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

See last page of advertisement revised prescribing information.

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN® Brand of
CONJUGATED ESTROGENS TABLETS, U.S.P.

Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration; however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al.*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)
No. 865—Each *purple* tablet contains 2.5 mg, in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg, in bottles of 100 and 1,000.

References: 1. Smith, D.C., Prentice, R., Thompson, D.J. and Herrmann, W.L.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. *293*:1164-1167, 1975. 2. Ziel, H.K., and Finkle, W.D.: Increased risk of endometrial carcinoma among users of conjugated estrogens, N. Engl. J. Med. *293*:1167-1170 1975. 3. Mack, T.M., Pike, M.C., Henderson, B.E., Pfeffer, R.I. Gerkins, V.R., Arthur, M., and Brown, S.: Estrogens and endometrial cancer in a retirement community, submitted for publication.
7642

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
contains natural estrogens exclusively

Nonstressed fetal heart rate monitoring in the antepartum period

FRANCE ROCHARD, M.D.
BARRY S. SCHIFRIN, M.D.
FRANCOISE GOUPIL, M.D.
HELENE LEGRAND, M.D.
JOSETTE BLOTTIERE, M.D.
CLAUDE SUREAU, M.D.
Paris, France, and Boston, Massachusetts

The role of nonstressed monitoring of the fetal heart rate (HR) in determining fetal well-being during the antepartum period was assessed in 125 high-risk patients. Observations on HR, variability, and HR response to fetal movement (FM) and uterine contractions (UC) over a 30 minute period were made with an external microphone and tocotransducer. A total of 625 tests were performed; the earliest gestation tested was 28 weeks, and the latest was 46 weeks. A reactive pattern (variability > 6 b.p.m. and accelerations with FM) appears to be a reliable indicator of fetal well-being. All the 51 fetuses exhibiting this pattern survived. This group also had the lowest incidence of neonatal complications. On the other hand, of the babies who failed to show variability > 6 b.p.m. or accelerations with FM (nonreactive pattern), 40 per cent died in the perinatal period. Thirty-five patients showed features of both a reactive and nonreactive pattern (combined pattern). Poor outcome in this group was confined to those in whom the majority of the pattern was nonreactive. An undulating HR pattern with virtually absent variability (sinusoidal pattern) was found in 20 Rh-sensitized fetuses, 50 per cent of whom died in the perinatal period. Bradycardia and tachycardia were not found to be reliable signs of fetal distress antepartum. Of the 12 fetuses who died during observation, six showed late decelerations with spontaneous UC but all showed diminished variability. The close correlation between nonstressed patterns and neonatal outcome demonstrated by this preliminary study warrants further use of this technique for fetal evaluation. (AM. J. OBSTET. GYNECOL. 126: 699, 1976.)

From Clinique Baudelocque, Service of Professor Lepage, Universite Rene Descartes, Paris, and the Department of Obstetrics and Gynecology, Harvard Medical School, Beth Israel Hospital, Boston.

Received for publication December 10, 1974.

Revised May 21, 1976.

Accepted June 17, 1976.

Reprint requests: Dr. Barry S. Schifrin, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90048.

OBSTETRICIANS HAVE long searched for methods of antepartum fetal evaluation that would be noninvasive and accurate and yield results that were immediately available. Ideally, the test should also be repeatable and incur minimal expense and inconvenience. While many biochemical and biophysical measurements have been proposed for antepartum fetal evaluation, few of these measurements have reliably predicted fetal outcome and even fewer have been shown to improve

Table I. Antepartum monitoring pattern classification

Pattern	*No.*
Reactive	51
Stable heart rate (120-160 b.p.m.)	
Variability > 6 b.p.m.	
Acceleration with fetal movement	
Nonreactive	19
Stable heart rate (120-160 b.p.m.)	
Variability < 6 b.p.m.	
No accelerations with fetal movement	
Sinusoidal	20
Stable heart rate (120-160 b.p.m.)	
Variability < 2 b.p.m.	
Sinusoidal pattern	
Frequency 2-5 per minute	
Amplitude 5-10 b.p.m.	
Combined	35

perinatal outcome when they were tested in a controlled setting.

Others as well as our group have shown a close correlation between fetal heart rate patterns during labor and neonatal outcome.[1, 2] Both this correlation and the availability of techniques for electronic monitoring of fetal heart rate and uterine activity from the maternal abdominal wall have prompted the application of this surveillance technique to the antepartum period. One approach has resulted in the development of the contraction stress test or oxytocin challenge test. Here, the heart rate pattern in response to induced or spontaneous uterine contractions has been shown to reliably predict fetal well-being.[3, 4]

In this study, we have adopted an approach first promulgated by Hammacher[6] and then by Kubli and associates[5] involving nonstressed monitoring of the fetal heart rate and uterine activity in the antepartum period. We present here our encouraging experience with this surveillance technique.

Material and methods

Population. Patients were drawn from both private and clinic populations of the Clinique Baudelocque in Paris, France. This facility is a referral center for Rh-isoimmunization problems in pregnancy which explains the large number of such patients in the study. Patients classified as having "threatened premature labor" were those admitted in labor before 37 weeks. In 15 of these, contractions ceased spontaneously. The remaining eight patients received uterine relaxants to inhibit contractions. Only two of the 23 patients progressed to delivery. Patients classified as having "suspect postmaturity" had gestations of greater than 42 weeks by conventional clinical criteria. The designation "premium baby" was applied in a group of women in whom social or demographic factors suggested increased risk of poor outcome, for example, the elderly primigravida. In the latter three groups, there were no obvious obstetric or medical problems. The miscellaneous group included three patients with previous fetal loss and one each with hyperemesis, kidney stones, anemia, hydramnios, jaundice of pregnancy, and mitral insufficiency.

Because one of our goals was to determine the relationship between nonstressed heart rate patterns and neonatal outcome, it was important that intervention not be influenced by test results. Thus, in the beginning of the study, the results were not made available to the physicians managing the patient. Patient management was based on clinical data and laboratory tests, including 24 hour urinary estriol determinations and biochemical analysis of anniotic fluid where indicated. As the study progressed, it was no longer possible to prevent intervention on the basis of these patterns. Ideally, intervention studies should be considered only if it can be shown that nonstressed heart rate patterns predict fetal outcome.

Technique. Heart rate and uterine activity patterns were obtained with a microphone transducer and a tocodynamometer combined in the Hewlett-Packard cardiotocograph.* Patients were maintained in the semi-Fowler position on a comfortable bed. Fetal movement was detected as a transient rise on the uterine contraction channel and confirmed by palpation or questioning of the patient.

Recordings were continued for at least 30 minutes. This minimal time was chosen because of data suggesting that fetuses undergo sleep-wake cycles about 20 minutes in length.[7] Recording for 30 minutes would hopefully assure us of at least a brief period of fetal wakefulness.

Classification of heart rate patterns. Records were analyzed for base-line heart rate, variability, and the heart rate response to spontaneous contractions and fetal movements (Table I). Heart rate patterns were classified as reactive, nonreactive, sinusoidal, and combined. A "reactive" heart rate pattern demonstrated a stable base-line rate usually between 120 and 160 beats per minute. The range of base-line variability was six beats per minute or greater, and accelerations accompanied fetal movement (Fig. 1). "Nonreactive" patterns were characterized by a stable base-line heart rate usually between 120 and 160 beats per minute (Fig. 2). However, the variability was consistently less than six beats per minute, and there were no accelerations with fetal movement. Patterns were characterized as

*Hewlett-Packard Co., Waltham, Massachusetts.

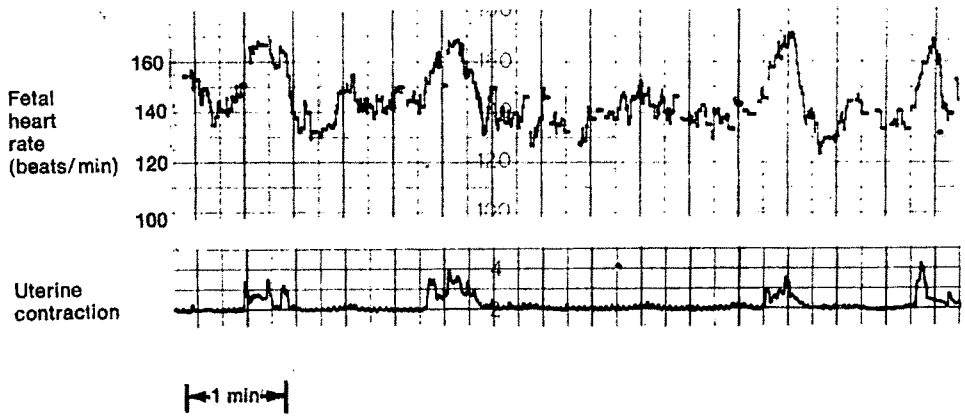


Fig. 1. Reactive heart rate pattern. The heart rate is stable at about 130 beats per minute. Variability is about 10 beats per minute, and accelerations accompany fetal movement.

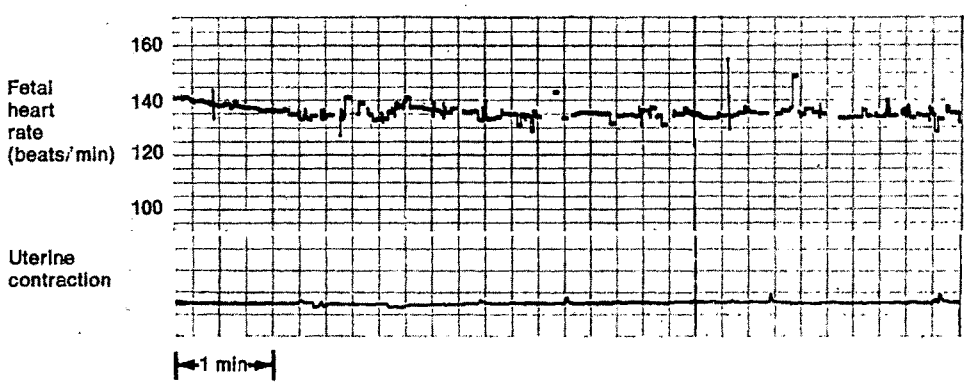


Fig. 2. Nonreactive heart rate pattern. The heart rate is stable at about 130 beats per minute. Variability is less than two beats per minute, and accelerations do not accompany fetal movement.

"sinusoidal" when periodic oscillations in the heart rate were superimposed on a nonreactive pattern (Fig. 3). The frequency of these fluctuations varied from two to five per minute, and the amplitude ranged from five to 10 beats per minute. "Combined" heart rate patterns revealed combinations of both reactive and nonreactive heart rate patterns (Fig. 4).

Measures of outcome. The measures of outcome utilized in this report were: (1) fetal survival or death; (2) presence or absence of fetal distress during labor; and (3) prolonged neonatal hospitalization (at the Clinique Baudelocque, parturients are confined to the hospital for six days after delivery; for the purpose of this report, prolonged neonatal stay denotes hospitalization of the neonate beyond six days of life); (4) presence or absence of stigmas of intrauterine growth retardation (birth weight less than the tenth percentile for gestational age), respiratory distress syndrome, or fetal anemia (fetal cord hemoglobin less than 13 gm. per cent).

These measures of outcome were used to test the null hypothesis that knowledge of nonstressed fetal heart rate patterns in the antepartum period cannot be used to predict fetal outcome.

Results

A total of 641 recordings were obtained for these 125 patients. The earliest gestation at which monitoring was performed was 25 weeks, and the latest was 44 weeks. The greatest number of tests in one patient was 30 and the least number was one; the average was five. The indication for nonstressed monitoring in 125 patients according to interpretation of the nonstressed pattern is indicated in Table II. The perinatal outcome according to heart rate pattern is presented in Table III. Of the 51 babies with persistently reactive patterns, 41 (80 per cent) tolerated labor without distress, were delivered in good condition, and had a normal follow-up. Six babies (12 per cent) developed fetal distress during labor, and four were affected with intrauterine

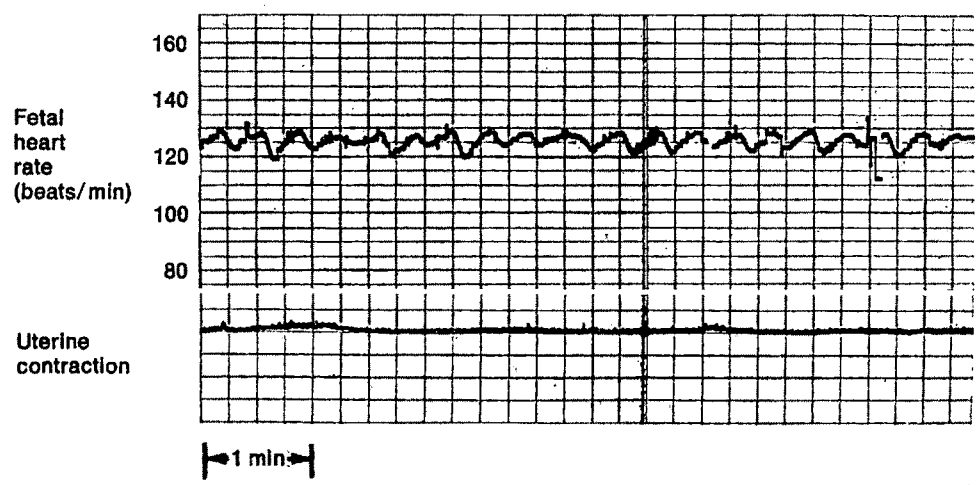


Fig. 3. Sinusoidal heart rate pattern. The heart rate is stable at about 130 beats per minute. The short-term variability is less than two beats per minute. The amplitude of the sinusoid is about 10 beats per minute, and the frequency is two cycles per minute.

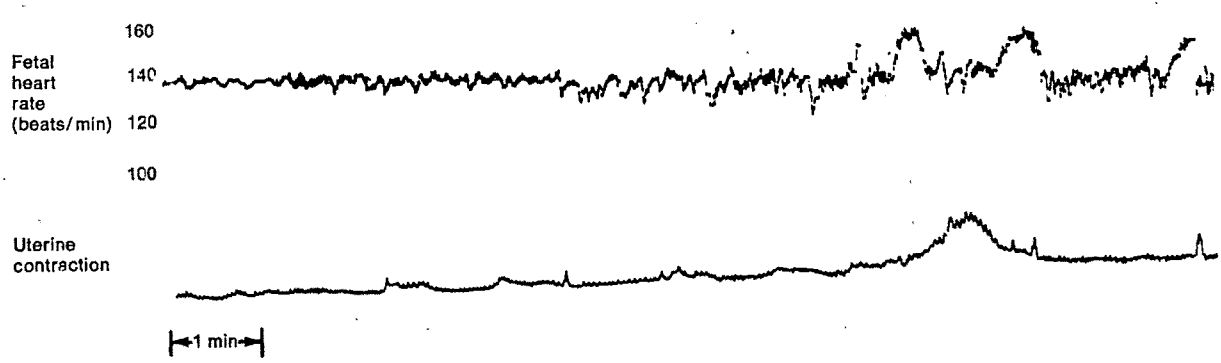


Fig. 4. Combined heart rate pattern. Pattern illustrates features of both nonreactive and reactive patterns.

growth retardation, the respiratory distress syndrome, or anemia. All of the infants with persistently reactive tests survived.

Of the 19 fetuses demonstrating persistent nonreactive patterns, five (26 per cent) died in utero or in the neonatal period, eleven (58 per cent) required prolonged neonatal care, and only three of the 19 were mildly affected or had fetal distress from which they recovered during labor. None of these babies was unaffected. The majority of these babies were found to be severely affected as a result of maternal Rh isoimmunization. Four had the respiratory distress syndrome.

Sinusoidal heart rate patterns were observed only in babies with severe isoimmunization. Of the 20 babies manifesting sinusoidal heart rate patterns, 10 (50 per cent) died either in utero or in the neonatal period, an additional eight (40 per cent) required prolonged hospitalization. Eighteen of the 20 had moderate to severe hydrops. Only two of the 20 babies with sinusoidal patterns survived without benefit of prolonged neonatal care.

Combined patterns were found in 35 patients. To assist in the evaluation of combined patterns, the duration of each component in each 30 minute record was calculated and compared to the outcome. For the 17 babies with a poor outcome, the mean percentage of nonreactive pattern was 55 per cent. For the 18 babies who did well at birth, nonreactive patterns accounted for 31 per cent of the recording time, on the average. To further facilitate analysis of combined patterns, we arbitrarily divided these records according to the predominant pattern. Nine of 10 fetuses (90 per cent) demonstrating nonreactive heart rate patterns for

Table II. Antepartum patterns

Patient population	Pattern				Total
	Reactive	Combined	Nonreactive	Sinusoidal	
Rh isoimmunization	6	10	14	20	50
Threatened premature labor	18	5	–	–	23
Toxemia	10	8	2	–	20
Diabetes	5	5	–	–	10
Suspect postmaturity	4	2	1	–	7
Miscellaneous	8	25	2	–	15
Total	51	35	19	20	125

Table III. Perinatal outcome according to nonstressed heart rate pattern

Outcome	Nonstressed heart rate pattern					Total
	Reactive	≥50% Reactive	<50% Reactive	Nonreactive	Sinusoidal	
Good outcome	41	16	1	0	0	58
Mildly affected	6	5	4	3	2	20
Prolonged neonatal care	4	4	4	11	8	31
Fetal death	0	0	1	4	8	13
Neonatal death	0	0	0	1	2	3
Total	51	25	10	19	20	125

Table IV. Perinatal outcome according to predominant pattern

Predominant pattern	Perinatal outcome			Total
	Good	Prolonged care	Death	
Reactive and ≥50% reactive	68	8	0	76
Nonreactive, sinusoidal, and <50% reactive	10	23	16	49
Total	78	31	16	125

more than 50 per cent of the recording (<50 per cent reactive) died in utero or required prolonged hospitalization. On the other hand, 80 per cent of babies in whom the predominant pattern was reactive (≥50 per cent reactive) did well.

When the various categories were combined into the reactive group (reactive and ≥50 per cent reactive) and the nonreactive group (nonreactive, sinusoidal, and <50 per cent reactive), an even more striking correlation with outcome was shown (Table IV). During the study, no fetus went from a reactive to a persistently nonreactive pattern. On six occasions, patterns were interpreted as nonreactive for the period of observation but became reactive with further testing or subsequent tests. These patients were listed in the reactive group.

Little correlation could be demonstrated between base-line fetal heart rate or variability and weeks of gestation. Also we did not find any strong predictive correlation between base-line tachycardia or bradycardia and outcome (Table V). Of the six babies with base-line rates ≥160 beats per minute, three did well, one died in utero, and three developed fetal distress during labor. The four babies with heart rates consistently below 120 beats per minute did well.

Spontaneous decelerations (usually variable decelerations) without contractions were found in 13 patients. Uterine contractions were present in 61 per cent of the tracings, the frequency increasing with advancing gestational age. Of the 77 patients exhibiting uterine activity, fetal decelerations were found in 23. While decelerations with contractions, especially late decelerations, were found more frequently in severely affected babies, the presence or absence of decelerations did not improve the predictive accuracy of the underlying heart rate pattern (Table VI). Late decelerations with spontaneous contractions were found only with nonreactive heart rate patterns.

During the period of study, 12 fetuses died under observation. While the mean heart rate in this group of babies was higher than in survivors, none demonstrated frank bradycardia, and only one showed tachycardia. Contractions were present in each case, but only seven of 12 demonstrated late decelerations. Without exception, however, there was a progressive diminution in beat-to-beat variability in the base-line heart rate as death approached.

Table V. Antepartum monitoring: Relationship between base-line rate and outcome

Base-line rate	*No.*
Tachycardia (>160 b.p.m.)	6
Good outcome	3
Intrauterine death	1
Fetal distress during labor	2
Bradycardia (<120 b.p.m.)	4
Good outcome	3
Rh isoimmunization—mildly affected	1

Table VI. Outcome according to pattern and presence of periodic deceleration

Pattern	*Records with periodic decelerations*	*Records without periodic decelerations*
Reactive	4 Good outcome—3 (75%)	24 Good outcome—18 (75%)
Non-reactive	14 Severely affected—14 (43%) Perinatal death—6	15 Severely affected—14 (42%) Perinatal deaths—5
Combined	5 Good outcome—3 (60%)	15 Good outcome—8 (47%)

Eight infants (10.5 per cent) of the 76 patients of the predominantly reactive group were premature by birth (birth weight less than 2,500 grams). Three of these developed the respiratory distress syndrome but survived. Of the 36 babies of the predominantly nonreactive group who were born alive, six (16.6 per cent) were premature by birth weight. Three of these developed the respiratory distress syndrome, and two died.

Comment

The results suggest that reactive heart rate patterns in the antepartum period indeed reflect fetal well-being. Of the 76 high-risk fetuses in whom the predominant heart rate pattern was reactive (reactive and ≥50 per cent reactive), only 8 (10.5 per cent) required prolonged neonatal stay and all survived. Of the 49 fetuses with predominantly nonreactive patterns (nonreactive, sinusoidal, and ≤50 per cent reactive), 23 (47 per cent) required prolonged neonatal care and 20 more (41 per cent) died either in utero or in the neonatal period. All of the babies who died in utero demonstrated progressive loss of variability; none had reactive patterns.

The benignity of the reactive pattern is supported by data from base-line recordings of heart rate and uterine activity preceding contraction stress testing.[3] Schifrin and colleagues[2, 3] reported that when accelerations with good variability were present no fetus developed late decelerations during the stress of induced contractions. Lee and co-workers[4] have also concluded that accelerations with fetal movement are a reliable sign of fetal well-being. Kubli and associates[5] and Hammacher[6] have made similar claims for "good variability" without specifying accelerations with fetal movement.

The testing procedure proposed here is perhaps the simplest form of antepartum heart rate evaluation. A microphone and a tocodynamometer are applied to the maternal abdominal wall, and observations on heart rate, uterine activity, and fetal movement are carried out. The results are immediately available, and the test can be repeated frequently or continued indefinitely.

Neither stress nor stimulus is provided in this test. It is believed that both normal and pathologic fetuses produce characteristic heart rate patterns, but there is no clear-cut separation of respiratory and nutritive function of the placenta as has been proposed for the contraction stress test.[6] Monitoring the fetus in this way seeks to uncover the presence or absence of an adequate central nervous system influence on the heart rate pattern.

As gestation advances, the fetal heart rate decreases and variability increases.[8] This likely represents an increasing influence of the fetal central nervous system, especially the vagus, on the heart rate.[9] Near term the normal fetus characteristically shows good variability (>10 and <25 beats per minute), a stable heart rate (between 120 and 150 beats per minute), and accelerations with fetal movement (reactive pattern).

A useful feature of antepartum testing is the fetal heart rate response to spontaneous contractions. The frequency of contractions increases with advancing gestation. Ruttgers and colleagues[8] have found that the frequency of contractions is less than three in 10 minutes until 36 to 37 weeks of pregnancy but increases progressively thereafter. At the thirtyeighth week, 80 per cent of the patients tested demonstrated spontaneous uterine activity.

Mild variable-type decelerations with or without accompanying uterine contractions occur in about 10 per cent of normal fetuses; late decelerations in response to contractions generally do not occur. In the normal fetus there may be periods of decreased variability which usually last less than 30 minutes. It is believed that these episodes represent fetal sleep-wake or rest-activity cycles and do not signify fetal compromise. Compromised fetuses show persistently decreased variability, absence of accelerations with movement (nonreactive pattern), and late or undefined decelerations with contractions. Resting heart rates in these

fetuses are usually within the normal range. The loss of beat-to-beat variability appears to represent blunting of the homeostatic mechanisms for control of heart rate. There is an increased likelihood of late decelerations during spontaneous contractions in these fetuses.

An undulating heart rate with virtually absent beat-to-beat variability (sinusoidal pattern) appears to be an ominous extention of the nonreactive pattern. The majority of babies with such patterns have died in utero or have been hopelessly compromised at birth.[10] This pattern likely represents a virtual absence of central nervous system control over the heart rate.

Sinusoidal patterns were found in nine of 12 fetuses prior to death in the series reported by Kubli and associates. Of the 20 fetuses demonstrating this pattern in this series, 50 per cent died in utero or in the neonatal period, and an additional 40 per cent required prolonged hospitalization after birth. Only 10 per cent of babies with a sinusoidal pattern had an uncomplicated course. Manseau and colleagues[10] as well as our group have found sinusoidal patterns in only those fetuses severely affected with Rh isoimmunization. In the series reported by Kubli and associates[11] the sinusoidal pattern occurred in a more diverse group.

Sinusoidal patterns found during labor have not been clearly related to asphyxia.[12]

Repeated nonstressed testing in a group of fetuses who were to die in utero has provided insight into the sequence of changes which precede fetal death. In serial tracings prior to death, the most consistent feature has been a progressive loss of base-line beat-to-beat variability in fetal heart rate patterns. No fetus with good variability died unexpectedly. Although base-line tachycardia has been observed more frequently in babies who are about to die, in the majority, the base-line levels are within the normal range. Base-line tachycardia is neither a reliable nor a constant sign of severe antepartum fetal hypoxia or impending fetal death. Persistent bradycardia has been the least commonly observed of all the monitoring patterns. It was observed in only one instance in a series of 12 antepartum deaths reported by Kubli and associates and in none of the cases reported here. It may be concluded that base-line bradycardia is not an early sign of fetal hypoxia or impending fetal death.

Kubli and associates[11] found that the presence of late decelerations was a most consistent sign of severe fetal hypoxia and impending death. He found decelerations in 91 per cent of the records with contractions in the premorbid group compared to only 10 per cent of those in the control group. We have also found a similar high incidence of decelerations in the babies in the nonreactive group. The combination of a nonreactive pattern and late decelerations with spontaneous contractions invariably presaged an ominous outcome in this study.

These studies, in general, support the conclusions of Martin and colleagues[13] and Hobel and co-workers[14] who have shown that ominous heart rate patterns during labor are associated with an increased risk of death from respiratory distress in the neonatal period.[13, 14] While the incidence of respiratory distress in the predominantly reactive and predominantly nonreactive groups was similar, death occurred only in the nonreactive group. However, the numbers are quite small.

In summary, nonstressed surveillance of the fetal heart rate in late pregnancy appears to provide reliable, predictive information about the fetal condition. The results of these studies warrant widespread utilization of this test in controlled studies to determine its effect in improving perinatal outcome.

REFERENCES

1. Hon, E. H.: Detection of fetal distress. Fifth World Congress of Gynaecology and Obstetrics, September, 1967, Sydney, Australia. London 1967, Butterworth & Co., Ltd.
2. Schifrin, B., Dame, L.: J. A. M. A. **219:** 1322, 1972.
3. Schifrin, B., Doctor, G., Lapidus, M., et al.: Contraction stress test for antepartum fetal evaluation, Obstet. Gynecol. **45:** 433, 1975.
4. Lee, C. Y., DeLoreta, P. C., and O'Lane, J. M.: A study of fetal heart rate acceleration patterns, Obstet. Gynecol. **45:** 142, 1975.
5. Kubli, F. W., Kaeser, L., and Hinselmann, M.: Diagnostic management of chronic placental insufficiency, *in* Pecile, A., and Finzi, C., editors: The Foeto-placental Unit, Amsterdam, 1969, Exerpta Medica Foundation, pp. 323-339.
6. Hammacher, K.: The clinical significance of cardiotocography, *in* Huntingford, P., Huter, M., and Saling, E., editors: Perinatal Medicine, New York, 1970, Academic Press, pp. 80-93.
7. Dreyfus-Brisac, C., and Blanc, C.: Electroencephalogramme et maturation cerebrale, Encephale **45:** 205, 1956.
8. Ruttgers, H., Kubli, F., Haller, U., Bachmann, M., and Grunder, E.: Die antepartale fetale Herzfrequenc; I. Verhalten von Grundfrequenz, Fluktuation and Dezelerationen in Schwangerschaft, Z. Geburtshilfe Perinatol. **176:** 294, 1972.
9. Schifferli, P. Y., and Caldeyro-Barcia, R.: Effects of atropine and beta-adrenergic drugs on the heart rate of the human fetus, *in* Boreus, L., editor: Fetal Pharmacology New York, 1973, Raven Press.
10. Manseau, P., Vaquier, J., Chavinie, J., and Sureau, C.: Le rythme cardiaque foetal sinusoidal. Aspect evocateur de

souffrance foetale au cours de la grossesse, J. Gynecol. Obstet. Biol. Reprod. **1:** 343, 1972.
11. Kubli, F., Ruttgers, H., Haller, U., Bogdan, C., and Ramzin, M.: Die antepartale fetale Herzfrequenz; II. Verhalten von Grundfrequenz, Fluktuation und Dezerationen bei antepartalem Fruchttod, Z. Gerburtshilfe Perinatol. **176:** 309, 1972.
12. Schifrin, B. S.: Unpublished data.
13. Martin, C. B., Siassi, B., and Hon, E. H.: Fetal heart rate patterns and neonatal death in low birthweight infants, Obstet. Gynecol. **44:** 503, 1974.
14. Hobel, C. J., Hyvarinen, M., and Oh, W.: Abnormal fetal heart rate patterns and fetal acid-base balance in low birth weight infants in relation to respiratory distress syndrome, Obstet. Gynecol. **39:** 83, 1972.

Serum levels of human placental lactogen and human chorionic gonadotropin in early pregnancy: A maturational index of the placenta

LOUIS L. PEETERS, M.D.*
JAMES A. LEMONS, M.D.
GORDON D. NISWENDER, PH.D.
FREDERICK C. BATTAGLIA, M.D.
Denver, Colorado

Between weeks 10 and 20 of gestation, there are rapid and opposing changes in blood levels of two hormones produced by the syncytiotrophoblast: hPL increases and hCG decreases. In this study, the relationship between these two changing hormone levels was examined, rather than the serum concentrations themselves, as a potential test for placental maturation. The relationship between the hCG and hPL concentrations and GA determined in a selected group of patients was described by the following equation: GA (in days) =97.3 + 24.8 ln [hPL] − 14.5 ln [hCG]. The endocrine evaluation of placental maturation by comparison of [hCG] and [hPL] in early pregnancy shows promise as a simple, safe, and inexpensive clinical tool for GA assessment.
(AM. J. OBSTET. GYNECOL. 126: 707, 1976.)

IN RECENT years there has been a delineation of the pre- and postnatal problems associated with deviations in intrauterine growth rate. In addition, there has been an increased cautiousness in obstetrics to avoid inadvertant delivery of a preterm baby. Thus, the prenatal assessment of gestational age (GA) has assumed increasing importance. Approximately 15 per cent of all pregnancies in a general population are characterized by unreliability of dates.[1] Therefore, a concern in obstetrics has been to develop methods for determining the chronological age of the fetus. Although chronological age should not be equated with either maturation of individual organ systems or the synchronized maturation of the total organism, it is important as an indication of both.

It is surprising that the dramatic changes in hormone levels which occur during early pregnancy have never been evaluated as predictors of placental maturation and thus, indirectly, of GA. Between weeks 10 and 20 of gestation, rapidly increasing hPL concentrations ([hPL]) are coupled with decreasing hCG concentrations ([hCG]).[2, 3] Because there is great inter- and intraindividual variation of these hormone concentrations, the measurement of the concentration of either hormone alone cannot be used to predict the duration of pregnancy nor the degree of placental maturation.[3, 4] However, measurement and comparison of the levels of these two hormones has not yet been evaluated in pregnant women. Since concentrations of both hormones are changing rapidly, and in opposite directions, the ratio of the two concentrations may be a sensitive index of placental maturation. This study was designed to examine the reliability and accuracy of a method which considers levels of these two hormones in relation to each other—rather than each

Division of Perinatal Medicine, Departments of Pediatrics, Obstetrics-Gynecology, and Physiology, University of Colorado Medical Center, and Department of Physiology and Biometrics, Colorado State University.

This work was supported in part by National Foundation–March of Dimes Grant CRBS-302, Public Health Service Research Grant HD-00781, and Public Health Service Training Grant HD-00429.

Received for publication February 23, 1976.

Accepted May 19, 1976.

Reprint requests: Dr. Louis L. Peeters, University of Colorado Medical Center, Division of Perinatal Medicine, Container B-198, 4200 E. Ninth Ave., Denver, Colorado 80220.

**Dr. Peeters was supported by a Grant of the Stichting "De Drie Lichten," The Hague, Holland.*

Table I. Characteristics of patient groups

Group	Race		Age (yr.)			Parity		
	White	Black	15-19	20-24	25-29	1	2	3
A. Accurate dates	9	0	2	3	4	3	6	0
B. Unreliable dates	9	2	4	4	3	7	3	1

individually—in determining the degree of placental maturation, and thus indirectly the GA, in a population of women with very accurate last menstrual dates.

Materials and methods

Selection of patients. Twenty-five pregnant women receiving care at Colorado General Hospital's obstetric clinic were selected randomly. All women satisfied the following criteria: (1) the first prenatal visit was made no later than week 14 of gestation and (2) there were no complications with pregnancy at the time of initial evaluation. From these 25 women, a group of nine patients were selected who satisfied these additional criteria: (3) the menstrual cycle was regular within 2 days per cycle, (4) the pregnancy remained uncomplicated throughout the study, (5) the patient was followed throughout pregnancy, including parturition, and (6) the GA estimated from the examination of the neonate using the criteria of Dubowitz, Dubowitz, and Goldberg[5] was in agreement within ±1 week with the estimate based on the date of the last menstrual period (LMP).

Of the original 25 women, five patients were not included in the study for the following reasons: two developed pregnancy complications and three were lost to follow-up. Nine patients met the accurate-dates criteria (Table I), and the data from these patients (Group A) were used to evaluate the relationship between GA and combined hPL and hCG levels. To obtain an assessment of this test in an obstetric population with questionable LMP dates, 11 patients (Group B) were evaluated who had been rejected from the accurate dates group because of failure to meet criterion (3) or (6) (Table I).

Study period. The experimental period was chosen to include the time in gestation when maximal rates of change in hPL and hCG concentrations were occurring and included weeks 10 through 25 of gestation. Clinic visits were conducted every 2 weeks on all patients. Whenever possible, samples were drawn at the same hour and on the same day of the week. To avoid bias, no clinical assessment of GA was performed during study visits; the clinical course during this period of gestation was evaluated by the physicians responsible for the subject's care, independent from this study. At each of the patient's five to eight visits, 8 ml. of whole blood was collected from an antecubital vein. The blood was allowed to clot for 4 to 24 hours at a temperature of +4° C., followed by centrifugation for 15 minutes at 3,000 r.p.m. Then the serum was quickly frozen with acetone and dry ice and stored at −15° C.

Radioimmunoassay. All samples were analyzed at the same time in a single assay. hPL was measured in duplicate by a double-antibody radioimmunoassay[6] yielding an intra-assay variability of 6.2 per cent. Inhibition curves obtained with the addition of varying quantities of serum were parallel to the standard curve. Preparations of hTSH, hFSH, hLH, and hCG did not influence the estimation of [hPL]. Finally, exogenous hPL could be recovered quantitatively when varying quantities were added to serum. Reagents for the hCG radioimmunoassay were provided by the Pituitary Hormone Distribution Program. Measurement of [hCG] were performed in triplicate by a radioimmunoassay technique[7] giving an intra-assay variability of 6.5 per cent. This method is specific for hCG, with negligible luteinizing hormone cross-reactivity.

Neurologic examination of the neonate. All the neonates in this population were examined twice, between 24 and 48 hours after delivery, in order to estimate the GA by the technique of Dubowitz, Dubowitz, and Goldberg.[5] Using this technique, the actual age after conception can be determined with an error of ±10 days. All examinations were performed by the same neonatologist, without knowledge of the endocrine results.

Results

The hormone levels were determined a total of five times for each Group A patient, between 70 and 145 days of gestation (weeks 10 through 21) except for two samples which had to be obtained at week 23 of gestation. Figs. 1 and 2 represent the relationship between the GA and the natural logarithm (ln) of the [hCG] and [hPL], respectively, for the nine Group A patients. Data points from the same patients were connected. Using the data for each woman, a multiple linear regression line was estimated, with the GA as the dependent variable and the ln [hPL] and in [HCG] as the independent variables.[8] Regression lines for each patient are computed based on the assumption that the nine regression lines are normally distributed as represented in Fig. 3. An equation for the mean line can be calculated:

$$GA = 97.3 + 24.8 \ln [hPL] - 14.5 \ln [hCG] \quad (1)$$

Two sources of variability can be distinguished.

1. The residual variability around the individual

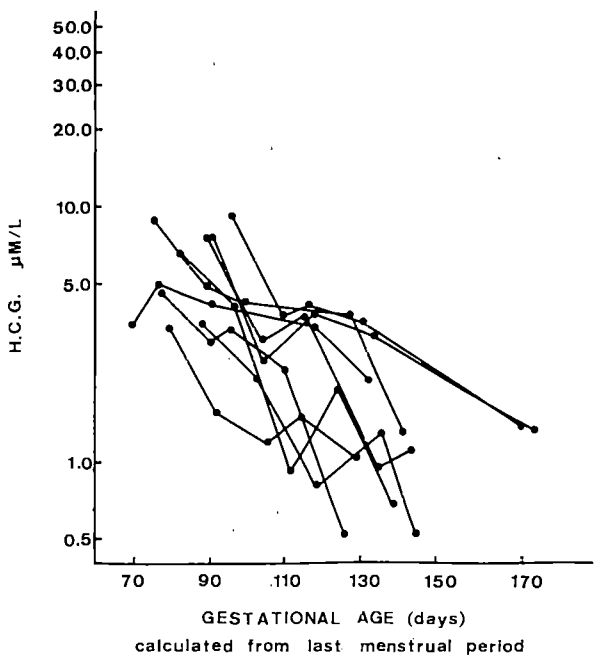


Fig. 1. Relationship between serum concentrations of hCG and gestational age in the nine Group A patients.

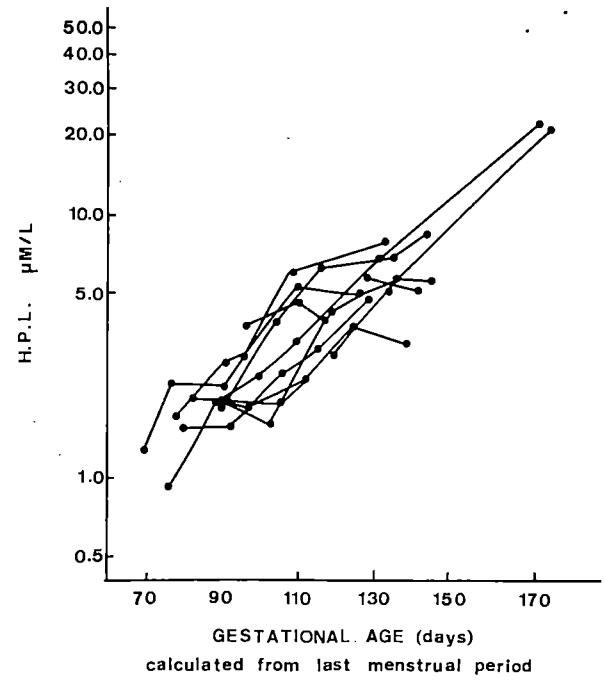


Fig. 2. Relationship between the serum concentrations of hPL and the gestational age in the nine Group A patients.

lines (described as variance S_1^2), determined by the following equation:

$$S_1^2 = \frac{2_{i=1}^{9} S_{1i}^2}{\text{d.f.}} \qquad (2)$$

where the number of degrees of freedom (d.f.) was obtained by multiplying the number of subjects times the difference between the number of observations per subject and the number of parameters in the regression d.f. = 9 × (5 − 3) = 18. According to Bartlet's test of homogeneity[8] the S_1^2 did not vary significantly among the nine subjects. Hence, these variances were pooled.

Using Eq. 2 the mean variance S_1^2 could be calculated:

$$S_1^2 = \frac{846}{18} = 46$$

2. The variability of the nine individual lines around the calculated mean line (described as variance S_2^2) was thought to be caused primarily by the variation in the intercept of each line, since comparison of the regression lines by applying analysis of variances[9] revealed no significant difference in the slopes. The magnitude of this type of variability was not equal over the whole study period of 70 to 145 days. The calculated variance was smallest between 85 and 120 days ($S_2^2 = 44$) but increased rapidly after 120 days of gestation ($S_2^2 > 50$).

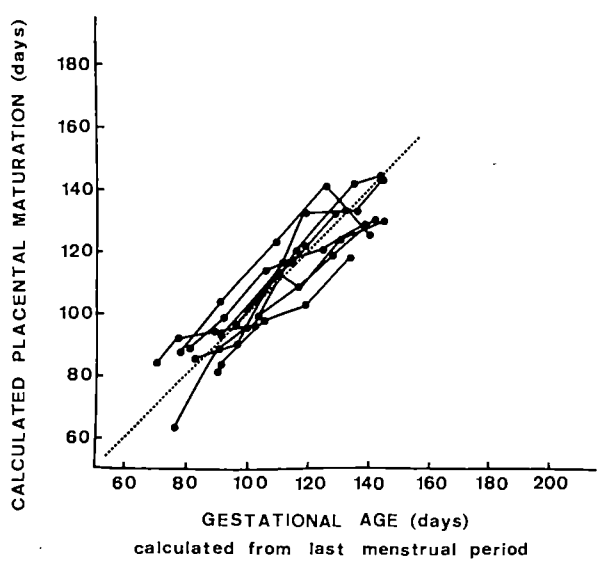


Fig. 3. Comparison of the placental maturation calculated with Eq. 1 (see text) vs. the gestational age in the nine Group A patients. The line of identity (.....) is included.

The two variances S_1^2 and S_2^2 can be combined by using the following equations:

$$S_T^2 = S_1^2 + S_2^2$$
$$S_T^2 = 46 + 44 = 90 \qquad (3)$$

resulting in a standard deviation (S.D.):

$$\text{S.D.} = \sqrt{S_T^2} = \sqrt{90} = 9.4 \text{ (days)}$$

Table II. Estimated gestational age in Group B patients using different techniques. All estimates are in days and are extrapolated to the day of delivery. The assumption has been made of a constant relationship between chronological age and organ maturation

Days after LMP	*Size of the uterus between weeks 10 and 14 of gestation*	*Physical exam of the mother 1 wk. prior to delivery*	*Endocrine estimate of placental maturation derived from single blood sample*	*Physical and neurologic maturation of neonate*
283	286	280	284	286
275	280	240	273	269
293	263	250	268	283
311	282	259	278	274
288	290	260	281	287
276	268	289	284	271
308	250	291	276	287
279	274	294	276	276
284	285	290	284	280
288	288	288	291	282
204	205	204	182	196

This S.D. applied only to the time interval from 85 to 120 days (12 to 17 weeks of gestation), where the second source of variability was smallest. A single sample, drawn from each of the nine accurate-dates patients at approximately 100 days of gestation, provided an estimate of GA which proved to be accurate within ±18.8 days (equal to ±2 S.D.).

In the 11 patients with unreliable dates, three different estimates of GA were compared: the clinical estimate derived from the physical examination of the mother 1 week prior to labor, the estimate derived from the endocrine assessment of placental maturation based upon a single blood sample obtained at approximately 100 days of gestation by dates, and an estimate from the pediatric examination of the newborn infant (Table II). Applying a paired t test, the endocrine estimate correlated significantly better with the neonate examination in this group of patients than did the estimate made by physical examination of the mother ($P < 0.05$).

Because the [hCG] were scattered and the [hPL] were clustered tightly during the period between 70 and 145 days, the question arose whether the level of hPL alone, in this particular time interval, would correlate better with the GA than the two hormone levels combined. From a linear regression with the GA as the dependent variable and the ln [hPL] as the independent variable the following equation for the Group A subjects was obtained:

$$\text{GA (in days)} = 68 + 36 \ln [\text{hPL}] \qquad (4)$$

The first source of variability (the residual variability around each subject's line; S_1^2) revealed a variance of 87. The second source (the variability of the nine individual lines around the calculated mean line; S_2^2) showed a variance of 65 in the period from 85 to 104 days of gestation (12 to 15 weeks—after 15 weeks, the variance increased very rapidly). By adding the two variances, the mean S.D. for the time period could be calculated for Eq. 4:

$$\text{S.D.} = \sqrt{S_T^2} = \sqrt{87 + 65} = 12.3 \text{ days}$$

Thus, use of hPL levels alone did not correlate as well with the GA as did the endocrine estimate of placental maturation using the two hormone levels determined simultaneously.

Comment

The chronological age of a fetus is an absolute which would be known with precision only if conception could be dated precisely. In an attempt to arrive at an estimate of chronological age of the fetus, physicians have relied upon measurements of variables which bear only an indirect relationship to chronological age. Such measurements include L/S ratios and creatinine concentrations in aminotic fluid, the size of the uterus, the growth of the fetal head as determined by ultrasound, etc. It should be emphasized that there is no reason why a test of maturation of organ function should correlate in any precise way with chronological age. The point can perhaps be made most vividly by considering the onset of puberty in childhood. In some children this may begin at 11 years of age; in others, at 14 years of age. One would not then conclude that their birth dates must be incorrect because puberty had not started at the "average" postnatal age. Similarly, in fetal and neonatal development, one should not expect that at the same chronological age children will show the same neurologic development, although this is precisely the assumption made in most attempts to estimate GA from the neonate examination.

The measurement and comparison of hCG and hPL

concentrations in *early* pregnancy has encouraging possibilities as a clinical tool. The method is simple, inexpensive, and safe for mother and fetus. Unfortunately, the estimate of GA thus obtained still has an error of approximately ±2½ weeks, when a single blood sample is used. However, this preliminary study may not indicate the true reliability of the combined hormone method for two reasons: (1) the number of subjects was small and (2) the reference point was not a precise knowledge of the date of conception, but rather an accurate LMP. Considering the variability in the time of ovulation from the first day of the LMP, this reference point has its own inherent error.

In this study, we have suggested that the rapidly falling concentration of hCG in early pregnancy, coupled with be rapidly increasing concentration of hPL may provide us some assessment of placental maturation and thus, indirectly, of GA. The assessment of placental maturation is important in its own right, whatever the usefulness of the derived estimate of GA.

Recently, Chatterjee, Baliga, and Munro[10] have shown that the in vitro rates of synthesis of hPL and hCG by placental membrane-bound polyribosomes change from weeks 10 through 40 of gestation. Thus, they have suggested that the changes in blood levels of these hormones reflect their relative rates of synthesis by the placental polyribosomes. This observation strengthens our assumption that the relative changes in blood levels of these two hormones may provide an assessment of placental maturation.

REFERENCES

1. Editorial: Lancet **1:** 132, 1972.
2. Jones, G. E. S., Delfs, E., and Stan, H. M.: Johns Hopkins Med. Bull. **75:** 359, 1944.
3. Teoh, E. S., Spellacy, W., and Buhi, W. C.: J. Obstet. Gynaecol. Br. Commonw. **78:** 673, 1971.
4. Johnson, J. W. C., Jr., and Odell, G. B.: Ann. Rev. Med. **24:** 165, 1973.
5. Dubowitz, L. Ms., Dubowitz, V. B., and Goldberg, C.: J. Pediatr. **77:** 1, 1970.
6. Niswender, G. D.: Unpublished data.
7. Vaitukaitis, J. L., Braunstein, G. D., and Ross, G. T.: Am. J. Obstet. Gynecol. **113:** 761, 1972.
8. Snedecor and Cochran: Statistical Methods, ed. 6, 1968, The Iowa State University Press, p. 296.
9. Hald, A.: Statistical Theory with Engineering Applications, New York, 1960, John Wiley & Sons, Inc. p. 579.
10. Chatterjee, M., Baliga, B. S., and Munro, H. N.: J. Biol. Chem. **251:** 2945, 1976.

Seminar on Anesthetic Management of the Surgical Patient

A seminar on Anesthetic Management of the Surgical Patient, sponsored by the Department of Anesthesiology, University of Miami School of Medicine, will be held during a Caribbean cruise aboard the S/S Royal Viking Sea, November 29–December 12, 1976. For further information, contact: Sonja Auxier, Department of Anesthesiology, University of Miami School of Medicine, P. O. Box 520875, Biscayne Annex, Miami, Florida 33152.

Combined obstetric and pediatric approach to prevent meconium aspiration syndrome

BONITA S. CARSON, M.D.
ROSALIND W. LOSEY, R.N.
WATSON A. BOWES, JR., M.D.
MICHAEL A. SIMMONS, M.D.
Denver, Colorado

Routine intrapartum pharyngeal suctioning with a DeLee catheter of infants with meconium staining has significantly reduced the incidence and severity of meconium aspiration syndrome (MAS). There have been no adverse sequelae to this procedure, which is carried out while the infant's head is on the perineum, prior to the onset of respirations. Routine suctioning of the trachea under direct vision after delivery is rarely necessary but should be done if meconium is visualized at the vocal cords. Tracheobronchial lavage with saline may add to the respiratory morbidity. No deaths or severe cases of MAS have occurred since institution of the obstetric suctioning procedure.
(AM. J. OBSTET. GYNECOL. 126: 712, 1976.)

MECONIUM aspiration syndrome (MAS) is a variety of aspiration pneumonia which occurs most frequently in term or post-term newborn infants who have passed meconium in utero. Affected infants often develop progressive respiratory failure with significant hypoxemia during the first 2 to 3 days of life. Death rates as high as 28 per cent have been reported for MAS.[1] Despite improvements in ventilation therapy and more recent developments in respiratory management,[2] therapy is often prolonged and ineffective once meconium aspiration is established. Therefore, prevention of the aspiration is potentially the most effective form of management of the syndrome.

Several studies have demonstrated the value of immediate postdelivery suctioning of the trachea under direct laryngoscopic visualization in reducing the incidence of MAS.[3-5] Bronchotracheal saline lavage after direct suctioning[6] and the use of corticosteroids[7] in the management of MAS have also been suggested. However, no technique which eliminates MAS has yet been reported.

Animal evidence suggests that MAS syndrome does not occur until the initiation of air breathing.[8] Therefore, complete removal of meconium prior to initiation of effective respirations might prevent the syndrome. Tracheal suctioning under direct laryngoscopic vision has been a standard part of our management of meconium staining. In May, 1974, intrapartum nasopharyngeal suctioning was added to our management. As soon as the baby's head appears on the perineum, and prior to the delivery of the shoulders, the obstetrician passes a DeLee suction catheter through the nares to the level of the nasopharynx and aspirates any mucus or meconium. He then suctions the mouth and hypopharynx in a similar manner. The delivery is then completed routinely. In the case of cesarean section, the procedure is the same: the infant is suctioned as soon as the head is delivered through the uterine incision, prior to delivery of the thorax.

The purpose of this study was to compare the effectiveness in the prevention of MAS of this combined obstetric and pediatric suctioning approach with the previous approach of direct tracheal suctioning alone.

From the Division of Perinatal Medicine, Departments of Pediatrics and Obstetrics-Gynecology, University of Colorado Medical Center.

Supported in part by United States Public Health Service Grants HD-00781 and HD-00429. Michael A. Simmons is an Established Investigator of the American Heart Association.

Received for publication April 22, 1976.

Accepted July 14, 1976.

Reprint requests: Michael A. Simmons, M.D., Department of Pediatrics, C-218, University of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colorado 80220.

Methods

The charts and computerized coding sheets of all infants born no earlier than 38 weeks of gestational age were reviewed to identify those infants who: (1) had meconium-stained amniotic fluid or skin; (2) had been coded as having a respiratory illness (pneumonia, aspiration, transient tachypnea, pneumothorax, or respiratory distress syndrome); and (3) had died or had illness significant enough to require more than 4 days of hospitalization. A diagnosis of MAS was made on the basis of presence of meconium in the trachea, subsequent respiratory distress, and an abnormal chest x-ray consistent with MAS.[9, 10] All babies who died with clinical MAS had the diagnosis confirmed histologically. The illness was judged "mild" if oxygen therapy was given for 48 hours or less at an inspired oxygen concentration no greater than 40 per cent. Patients who required more than 40 per cent oxygen or oxygen therapy for more than 48 hours but who did not require assisted ventilation were categorized as "moderately" ill. Those babies who required assisted ventilation or who died were termed "severe."

The patients were divided into three groups, according to the predominant management of meconium staining at the time of their deliveries:

Group I. July, 1970, through April, 1974: deep suctioning by obstetrician not done; suction under direct vision by pediatrician common but not invariable; tracheobronchial lavage not done.

Group II. May, 1975, through March, 1975: deep suctioning by obstetrician usually done; direct tracheal suctioning followed by tracheobronchial lavage routine.

Group III. April, 1975, to November, 1975 (prospective study): deep suctioning by obstetrician done consistently; suction under direct vision by pediatrician done, if indicated; lavage done on randomized basis.

During the Group III phase, three of the authors attended deliveries with the house staff to verify meconium at the level of the vocal cords. If meconium was present at the cords, the infant was promptly intubated and suctioned. If meconium was found below the cords at the time of intubation, the infant was lavaged on a random basis, informed consent having been obtained from the parents prior to delivery. Over the 6 month period, only two infants in Group III qualified for intubation according to the protocol.

Results

As shown in Table I, during the first study period (Group I, from July, 1970, until the obstetric procedure was introduced in May, 1974) there were 947 cases of meconium staining among 7,585 term births (incidence of 12.5 per cent). Of the infants with meconium staining, 18 developed MAS (incidence of 1.9 per cent), resulting in five deaths (MAS mortality rate of 28 per cent).

Table I. Comparison of the incidence and severity of MAS among three groups of infants in which meconium staining was managed differently

	Group I	*Group II*	*Group III*
Term births	7,585	2,320	1,681
Meconium staining (per cent incidence)	947 (12.5%)	381 (16.4%)	273 (16.2%)
MAS, total cases	18	7	1
Mild	9	4	1
Moderate	3	2	0
Severe	6	1	0
MAS deaths	5*	0	0

*Twenty-eight per cent of MAS cases (0.52 per cent of all with meconium staining).

During the second time period (Group II), when the obstetric suctioning had been instituted and pediatric suctioning under direct vision was almost invariable, there were 2,320 term births with 381 cases of meconium staining (incidence of 16.4 per cent). Seven of the 381 infants with meconium staining developed MAS (incidence of 1.8 per cent), but there were no deaths. Of the seven infants with MAS in Group II, only two were suctioned prior to delivery according to our protocol because of precipitate delivery or omission by the obstetrician. Each of the infants who was suctioned developed only mild MAS. The severe case of MAS during this time occurred in an infant who was not suctioned prior to delivery and who was intubated and given positive-pressure assisted ventilation before the trachea was suctioned.

Each of the seven infants with MAS in Group II received tracheobronchial lavage with normal saline. An additional five infants with meconium staining were identified who had no meconium in the trachea on direct visualization but who were nevertheless lavaged, with clear return. These five infants subsequently required oxygen (25 to 35 per cent) for 24 to 48 hours. All had chest x-rays interpreted as consistent with iatrogenic wet lung.[10, 11] Our clinical impression that the lavage procedure was increasing morbidity led to the prospective study of infants with meconium staining from April, 1975, to November, 1975 (Group III).

During the 6 month period when the prospective protocol was in effect, among 273 infants with meconium staining, only two infants were identified who had meconium present at the cords and who thus qualified for intubation. Only one of these infants devel-

Table II. Comparison of the three groups of infants with MAS with regard to hospital days, Apgar scores, and mode of delivery

	Group I	*Group II*	*Group III*
No. of patients with MAS	18	7	1
Mean hospital days of survivors	9.7	8.3	8
Intensive care	9.2	4.4	3
Low-risk nursery	0.5	3.9	5
Mean Apgar scores			
At 1 min.	4.7	5.1	5
At 5 min.	6.6	6.6	9
Mode of delivery			
Vaginal	15	6	1
Cesarean section	3	1	0

Table III. Protocol for combined obstetric and pediatric management

1. As soon as the baby's head appears on the perineum, the obstetrician passes a DeLee suction catheter through the nares to the level of the nasopharynx and aspirates any mucus or meconium, then suctions the mouth and hypopharynx
2. Immediately after delivery the pediatrician suctions the oropharynx with a bulb and, if meconium is present, inspects the cords by direct laryngoscopy while an assistant monitors the heart rate
3. If meconium is present at the cords, direct suctioning of the trachea with either a DeLee catheter or mouth–endotracheal tube is performed
4. Usual measures of ventilation and resuscitation are carried out

oped MAS (1/273 or 0.4 per cent), and his disease was mild. During this 6 month period, iatrogenic wet lung disease secondary to lavage did not occur.

With the use of both a binomial probability function and the Fisher exact test, the difference in incidence of MAS between Group I (no OB suction, no lavage) and Group III (OB suction, no lavage) was significant ($P < 0.05$). Group II was not included in this analysis due to the variable imposed by the introduction of lavage and the probability that lavage itself was contributing to the respiratory morbidity.

Statistical comparisons of retrospective data cannot establish cause-and-effect relationships. Such conclusions are particularly tenuous in areas of medicine undergoing rapid changes in techniques and approaches. Clearly, in our institution there has been a significant reduction in MAS incidence and severity associated with the introduction of intrapartum suctioning. A cause-and-effect relationship cannot be established definitively without a prospective, randomized clinical trial. In the 8 months since the completion of the study reported here, there have been no cases of MAS at our institution. Given the apparent risk-free benefit of this logical suctioning procedure, we do not feel that such a clinical trial would be justified.

Table II compares hospital days, Apgar scores, and mode of delivery among the three study groups of MAS babies. There were no differences in hospital days or in 1 minute Apgar scores among the three groups. The differences between Groups I and II in intensive-care days is partially accounted for by the availability of more sophisticated nursing care in the low-risk unit beginning in July, 1973. The introduction of obstetric suctioning, and the secondary small delay before completion of delivery, did not reduce the infants' Apgar scores. Table II shows that the Apgar scores among MAS infants were the same before and after the introduction of intrapartum suctioning. In addition, the mean Apgar scores among infants in Group III who did not develop respiratory morbidity were 7.4 at 1 minute and 8.9 at 5 minutes.

Comment

Gooding and associates[8] demonstrated in newborn puppies that two conditions must exist before MAS can occur: (1) meconium must be present in the trachea and (2) the animal must breathe. Although gasping in utero has been shown to occur with hypoxic stress,[12] the net amount of meconium-stained amniotic fluid inhaled in utero is probably not great enough to produce MAS. Indeed, these investigators were unable to produce MAS in their model with intrauterine gasping of meconium-laden amniotic fluid.[8]

Therefore, it is logical to remove meconium from the trachea before the infant breathes. While immediate tracheal suctioning after delivery has been shown to reduce the morbidity and mortality rates from MAS,[3–5] the addition of tracheal suctioning prior to delivery of the thorax further reduces the chance that MAS might occur. Our results demonstrate that thorough suctioning in this manner is effective in preventing the aspiration of meconium into the infant's trachea, since no effective gasping seems to occur even after delivery of the head onto the perineum. Indeed, in only two instances during our prospective study was meconium still present after the obstetric maneuver. This is in sharp contrast to the 56 per cent incidence of meconium in the trachea found by Gregory and associates[4] in babies who breathed prior to suctioning.

The presence of meconium at the cords has proved in our study to be a good guideline as to which infants should be intubated. Gregory and associates[4] reported a 10 per cent incidence of tracheal meconium in infants who had no supraglottic or pharyngeal meconium. We cannot state how many of our infants had tracheal meconium when the pharynx was clear, since we did

not routinely intubate and suction under such conditions; however, none of the 271 infants with no meconium in the pharynx developed MAS. Assuming the reported 10 per cent incidence of tracheal meconium in the absence of pharyngeal meconium,[4] the absence of MAS in such infants further substantiates the efficacy of the obstetric suctioning procedure. If the obstetric suctioning procedure is properly carried out, we feel that the risks of intubation are not warranted as long as meconium is not visualized at the cords.

Tracheobronchial lavage has been suggested as an adjunct in removing meconium.[5] The addition of this technique was not found to be beneficial in our series and, in fact, seem to increase morbidity. While it could be construed that "mild" MAS in Group II might have been worse if not for lavage, the substantial reduction in the cases of MAS and elimination of iatrogenic wet lung disease in Group III reinforces our clinical impression. The five infants without meconium demonstrable in their tracheas who were nevertheless lavaged all developed a mild respiratory illness with a distinctive chest x-ray. This suggests that lavage itself, in the absence of meconium, leads to respiratory morbidity which might be confused with MAS. One study has shown that if suctioning of the instilled saline is not performed immediately, ventilation is impaired.[5] On the basis of our retrospective analysis, we feel that bronchial saline lavage has no value in the management of meconium staining.

Manipulation of an infant's airway by deep suctioning, laryngoscopy, and intubation has often been discouraged because of the fear of laryngospasm and reflex bradycardia. We have not been able to document any sequelae of either the obstetric suctioning procedure or the pediatric management when properly performed. Gregory and associates[4] likewise did not report any untoward sequelae of the tracheal suctioning procedure.

Our current protocol for management of infants delivered to mothers with meconium-stained amniotic fluid is outlined in Table III. We would emphasize that in our hands the addition of the obstetric suctioning has been the most important factor leading to a decreased incidence of MAS and, when it is performed properly, usually eliminates any need for direct tracheal suctioning or lavage.

Conclusions

1. Deep suctioning of the nasopharynx prior to delivery of the thorax, coupled with tracheal suction under direct vision if meconium is still present in the hypopharynx, significantly reduces the incidence of MAS and effectively prevents severe MAS.

2. Routine tracheal suctioning is not necessary unless meconium is visible at the cords.

3. The addition of saline lavage to the suctioning procedures leads to increased morbidity.

REFERENCES

1. Vidyasagar, D., Yeh, T. F., Harris, V., and Pildes, R. S.: Assisted ventilation in infants with meconium aspiration syndrome, Pediatrics **56:** 208, 1975.
2. Fox, W. W., Berman, L. S., Downes, J.-J., Jr., and Peckham, G. J.: The therapeutic application of end-expiratory pressure in the meconium aspiration syndrome, Pediatrics **56:** 214, 1975.
3. Ting, P., and Brady, J. P.: Tracheal suction in meconium aspiration, AM. J. OBSTET. GYNECOL. **122:** 767, 1975.
4. Gregory, G. A., Gooding, C. A., Phibbs, R. H., and Tooley, W. H.: Meconium aspiration in infants—a prospective study, J. Pediatr. **85:** 848, 1974.
5. Burke-Strickland, M., and Edwards, N. B.: Meconium aspiration in the newborn, Minn. Med. **56:** 1031, 1973.
6. Burke-Strickland, M.: Tracheobronchial lavage in small infants, Minn. Med. **56:** 287, 1973.
7. Frantz, I. D., III, Wang, N. S., and Thach, B. T.: Experimental meconium aspiration: Effects of glucocorticoid treatment, J. Pediatr. **86:** 438, 1975.
8. Gooding, C. A., Gregory, G. A., Taber, P., and Wright, R. R.: An experimental model for the study of meconium aspiration of the newborn, Radiology **100:** 137, 1971.
9. Gooding, C. A., and Gregory, G. A.: Roentgenographic analysis of meconium aspiration of the newborn, Radiology **100:** 131, 1971.
10. Wesenberg, R. L.: The Newborn Chest, Hagerstown, Md., 1973, Harper & Row, Chap. 11, pp. 120-122.
11. Wesenberg, R. L., Graven, S. N., and McCabe, E. B.: Radiological findings in wet-lung disease, Radiology **98:** 69, 1971.
12. Dawes, G. S.: Revolutions and cyclical rhythms in prenatal life: Fetal respiratory movements rediscovered, Pediatrics **51:** 965, 1973.

Prenatal diagnosis of placental steroid sulfatase deficiency

GLENN D. BRAUNSTEIN, M.D.
FREDERICK H. ZIEL, B.A.*
ARTHUR ALLEN, M.D.
ROBERT VAN DE VELDE, PH.D.
MACLYN E. WADE, M.D.
Los Angeles, California

Placental steroid sulfatase deficiency is an unusual cause of low estriol production during pregnancy. Its importance lies in the differentiation of this disorder from the more ominous fetal defects that result in low estriol levels. Serum free estriol levels were found to be low or absent in a 25-year-old gravida 3, para 2 woman, while placental lactogen and chorionic gonadotropin levels were normal. An abdominal x-ray revealed no apparent congenital abnormalities and an oxytocin challenge test was negative. The dehydroepiandrosterone sulfate (DHEA-S) level in the patient's amniotic fluid was 6.8 to 18.4 times greater than those found in control amniotic fluids. The patient's amniotic fluid cortisol level was normal. Twenty-four hours following a normal, spontaneous labor and delivery at 39 weeks, the male infant underwent a synthetic ACTH$^{1-24}$ stimulation test, with serum cortisols rising from 3.7 to 46 μg/dl at 1 hour. The placenta was morphologically normal on gross, light, and electron microscopic examinations. Steroid 3-alcohol sulfatase and arylsulfatase activities in the patient's placenta were virtually absent. These data indicate that this benign cause of low serum estriol levels may be diagnosed prenatally by elevated amniotic fluid DHEA-S levels. (AM. J. OBSTET. GYNECOL. 126: 716, 1976.)

THE UTILIZATION of urine and serum estriol measurements in the management of high-risk pregnancies has been well established.[1, 2] Approximately 90 per cent of the estriol present in the maternal serum or urine is derived from placental conversion of steroid precursors produced in the fetus. Therefore, maternal serum or urine estriol levels reflect primarily the status of the "fetal-placental unit."[1] Very low maternal estriol levels are associated with fetal death, high-dose corticosteroid therapy, anencephaly, fetal adrenal hypoplasia, and placental steroid sulfatase deficiency. The first three disorders may be differentiated on clinical, historic, and radiographic grounds, whereas the latter two are difficult to distinguish from each other. Since fetal adrenal hypoplasia is associated with a high neonatal mortality rate,[3] a reliable prenatal method for discriminating between fetal adrenal hypoplasia and placental sulfatase deficiency would be desirable.

During the study of the pregnant patient described below, low serum and urinary estriol levels were found. A method for diagnosing placental steroid sulfatase deficiency antepartum was developed.

From the Departments of Medicine, Obstetrics and Gynecology, and Pathology, Cedars-Sinai Medical Center and U.C.L.A. School of Medicine.

Supported in part by United States Public Health Service Grant RR05468.

Received for publication October 14, 1975.

Revised May 10, 1976.

Accepted June 24, 1976.

Reprint requests: Glenn D. Braunstein, M.D., Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90048.

**Bioscience Enterprises Summer Student Research Fellow.*

Case report

A 25-year-old gravida 3, para 2 Spanish-American woman was first seen at the Cedars-Sinai Medical Center Obstetric Clinic at 10½ weeks of gestation. Her prenatal course was normal until 34.5 weeks of gestation, when a discrepancy between fundal size and gestational dates was noted. A serum estriol was found to be undetectable. At 36 weeks of gestation, a flat-plate radiograph of the abdomen revealed no apparent congenital abnormalities, and an oxytocin challenge test performed at 37 weeks did not indicate fetal distress. An amniocentesis was performed at 38½ weeks, and at

39 weeks the patient entered labor spontaneously with normal first and second stages of labor. A 7 pound 8 ounce male infant was delivered vaginally, with Apgar scores of 9 at both 1 and 5 minutes. A 588 gram placenta was delivered spontaneously. The mother's postpartum course was uneventful.

The male infant was judged to be normal by physical examination. His hospital course was complicated only by transient jaundice with a total bilirubin of 10.6 mg. per deciliter, indirect bilirubin of 8.8 mg. per deciliter, and direct bilirubin of 1.8 mg. per deciliter. Serum electrolytes were normal throughout the infant's hospital stay. At 24 hours of age 0.25 mg. of synthetic $ACTH^{1-24}$ (Cortrosyn) was injected intravenously Serum cortisol levels rose from a baseline of 3.6 μg per deciliter to 46 μg per deciliter at 1 hour.

The mother's family history was noncontributory. Her previous obstetric history revealed normal gestations, labor, and deliveries of male infants, 2 and 5 years prior to the above pregnancy.

Materials and methods

Radioimmunoassay. Serum estriol,[5] human chorionic gonadotropin (hCG),[6] human placental lactogen (hPL),* amniotic fluid dehydroepiandrosterone sulfate (DHEA-S),† and cortisol[8] levels were determined by radioimmunoassays. The steroid levels in the patient's amniotic fluid were compared to those present in three normal amniotic fluids obtained from pregnant women of comparable gestational age.

Placental sulfatase activities. Placental tissue obtained from the patient and two women with normal term deliveries were immediately frozen and stored at −20° C. At the time of analysis, the placentas were thawed, dissected free of membranes, washed with saline, and minced. Placental alcohol 3-steroid sulfatase activity was measured by the method of Townsley and associates.[9] DHEA-7(N)-^{3}H sulfate‡ (S.A. 4.6 Ci/mmol) served as a substrate and DHEA-4-C^{14}§ (S.A. 57.5 mCi/mmol) was used for recovery purposes.

Placental arylsulfatase activity was measured by the procedure described by Oakey and associates.[10] Estrone-6,7-^{3}H (N) sulfate§ (S.A. 45 Ci/mmol) and estrone-4-C^{14}§ (S.A. 52 mCi/mmol) were used as substrate and recovery steroids, respectively.

Urinary estriol. The method of Goebelsman[11] was used to measure urinary estriol in the 24 hour urine sample collected at 38 weeks of gestation.

*Human chorionic somatomammotropin Radioimmunoassay Kit, New England Nuclear Corporation, Boston, Massachusetts.

†Performed by Radioassay Systems, Inc., Carson, California.

‡Amersham-Searle Corp., Arlington Heights, Ill.

§New England Nuclear, Boston, Mass.

Table I. Maternal serum hCG, hPL, and estriol levels

Weeks of gestation	*hCG (I.U./ml.)*	*hPL (μg/ml.)*	*Estriol (ng./ml.)*
34.5	6.2	4.7	Undetectable
35	4.75	3.3	Undetectable
36.5	8.0	2.7	Undetectable
37	6.75	6.1	1.1 ng./ml.
37.5	7.625	4.8	1.1 ng./ml.
38.5	7.9	5.0	—
Normal	3.8-38.5	3.0-8.0	6.62-24.09

Table II. Amniotic fluid dehydroepiandrosterone sulfate

	DHEA-sulfate (ng./ml.)	*Cortisol (μg/ml.)*
Patient	450	4.6
Control No. 1	60	6.4
Control No. 2	60	5.2
Control No. 3	22	3.3

Placental morphology. The placental tissue obtained immediately after delivery was embedded in paraffin and stained with hematoxylin and eosin for light microscopic examination. One millimeter cubes of fresh placenta were fixed in cacodylate-buffered 3 per cent glutaraldehyde, postosmicated, dehydrated in graded series of acetones, and embedded in Epone 812. Following polymerization, orientation sections were cut at 1 μ and stained with Azure II in methylene blue. They were then examined with a Jeol 100B electron microscope.

Results

The estriol, placental lactogen, and chorionic gonadotropin levels in the maternal serum samples collected serially from 34.5 weeks of gestation until term are shown in Table I. The serum estriol levels were extremely low or undetectable; the placental lactogen and chorionic gonadotropin levels were normal. Twenty-four hour urinary estriol excretion was also low, at less than 2 mg. per 24 hours (normal = 21.5 ± 7.4 mg. per 24 hours).

The DHEA-S levels in the patient's amniotic fluid were 6.8 to 18.4 times greater than the three control amniotic fluids. At the same time the amniotic fluid coritsol level was normal (Table II). The patient's placenta was morphologically normal by both light and electron microscopy. The placental steroid alcohol 3-steroid sulfatase and arylsulfatase activities were virtually absent in the patient's placenta as compared to controls (Figs. 1 and 2).

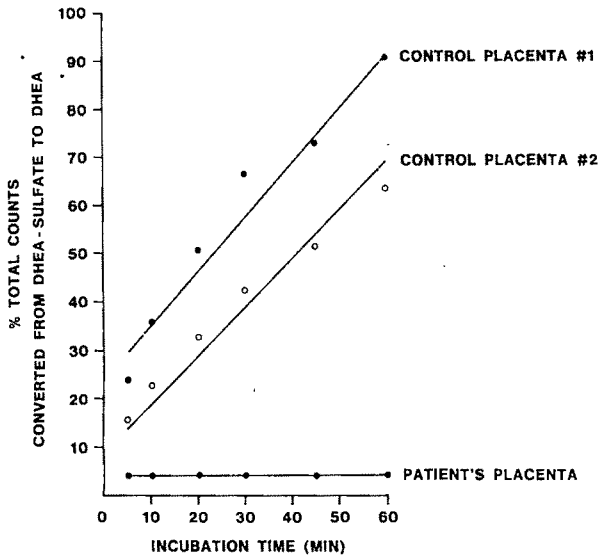


Fig. 1. Comparison of placental steroid 3-alcohol sulfatase activity determined by the per cent conversion of DHEA-S to DHEA during 60 minute incubations of the patient's placenta and two control placentas.

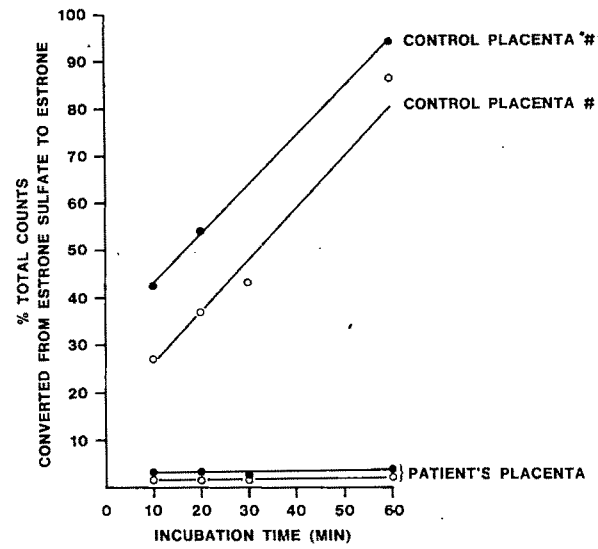


Fig. 2. Comparison of placental arylsulfatase activity determined by the per cent conversion of estrone sulfate to estrone during 60 minute incubations of the patient's placenta and two control placentas.

Comment

The absence of a history of maternal glucocorticoid ingestion in the patient described above eliminated the transplacental passage of corticosteroids, with their attendant suppression of the fetal hypothalamic-pituitary-adrenal axis, as the cause of the low maternal serum and urinary estriol levels. Similarly, the presence of normal fetal heart tones and the absence of discernible fetal malformations on abdominal x-ray of the mother removed fetal death and anencephaly from consideration. The elevated levels of amniotic fluid DHEA-S with a normal cortisol concentration suggested a block in the ability of the placenta to remove the sulfate from 16 OH-DHEA-S, the fetal precursor of estriol. Had fetal adrenal hypoplasia been present, both the DHEA-S and cortisol levels would be expected to be low. Additional evidence against congenital fetal adrenal hypoplasia was obtained by the normal rise in the serum cortisol level in the infant following adrenal stimulation with synthetic ACTH[1-24]. The presence of placental steroid sulfatase deficiency was confirmed by the extremely low levels of steroid alcohol 3-sulfatase activity in the patient's placenta.

Eleven pregnancies have been previously described in which the placenta was shown to be deficient in steroid sulfatase activity.[3, 10, 12-15] In an additional five pregnancies, this defect was suspected.[3, 14] The frequency of this enzymatic deficiency appears to be less than 1 in 5,000 pregnancies.[10] In primiparous women, this defect has been associated with prolonged gestation and occasionally an inability to induce labor. Multiparous women have usually undergone spontaneous labor and delivery. All the pregnancies resulted in the delivery of male infants, suggesting that this is an x-linked trait. Further support for the x-linked hypothesis has been provided by Oakey and associates.[10] They studied a patient whose first pregnancy was associated with placental sulfatase deficiency and delivery of a male infant; the second was characterized by normal urinary estrogen levels followed by the delivery of a female infant.

Since the placental enzyme responsible for hydrolyzing steroid alcohol-3-sulfates is different from that involved in the hydrolysis of arylsulfates,[16] the activity of the latter enzyme was also measured in our patient's placenta and was found to be extremely low. Other patients with similar, combined deficiencies of steroid and arylsulfatase activities have been reported.[10, 14, 15]

The major importance of placental steroid sulfatase deficiency is in the differentiation of this benign disorder from congenital adrenal hypoplasia. Neither human placental lactogen or chorionic gonadotropin is useful for this, since the production of both these placental proteins is not dependent upon placental steroid sulfatase activity, nor precursors of fetal adrenal origin. A DHEA and DHEA-S loading test has also been used to make a prenatal diagnosis of placental steroid sulfatase deficiency. France and associates[14] infused both of these substances into a pregnant woman who had demonstrated low urinary estriol excretion. The

DHEA resulted in a rise in urinary estrogen excretion, indicating normal placental aromatase activity. DHEA-S did not result in a significant increase in urinary estrogens. This indicated an inability to remove the sulfate from the precursor of estriol. More recently, Tabei and Heinrichs[15] noted an absence in rise of urinary estriol excretion in two women with placental steroid sulfatase deficiency after the intra-amniotic installation of DHEA-S. These loading tests as described require several days of urine collections, and are not generally available to clinicians in this country. Conversely, amniotic fluid may be easily obtained in the last trimester of pregnancy, carries little risk to the patient and fetus, and reference laboratories capable of measuring DHEA-S in the amniotic fluid are available.

Dr. Jeffrey Travis, City of Hope Medical Center, Duarte, California, kindly determined the human placental lactogen levels. The secretarial assistance of Mrs. Star Carter is gratefully acknowledged.

Addendum

Since submission of this manuscript, an additional patient with placental sulfatase deficiency has been described (Osathanondh, R., Canick, J., Ryan, K. J., and Tulchinsky, D.: Placental sulfatase deficiency: A case study, J. Clin. Endocrinol. Metab. 43: 209, 1976). An elevated DHEA-S level was also found in the amniotic fluid, confirming the results of the present study.

REFERENCES

1. Beischer, N. A., and Brown, J. B.: Current status of estrogen assays in obstetrics and gynecology. II. Estrogen assays in pregnancy, Obstet. Gynecol. Surv. **27:** 303, 1972.
2. Tulchinsky, D., Hobel, C. J., and Korenman, S. G.: A radioligand assay for plasma unconjugated estriol in normal and abnormal pregnancies, Am. J. Obstet. Gynecol. **111:** 311, 1971.
3. Fliegner, J. R. H., Schindler, I., and Brown, J. B.: Low urinary estriol excretion during pregnancy associated with placental sulphatase deficiency or congenital adrenal hypophasia. J. Obstet. Gynecol. Br. Commonw. **79:** 810, 1972.
4. Freeman, R. K.: The use of the oxytocin challenge test for antepartum clinical evaluation of uteroplacental respiratory function, Am. J. Obstet. Gynecol. **121:** 481, 1975.
5. Kao, M., Braunstein, G., Rasor, J., and Horton, R.: A simple radioimmunoassay for unconjugated estriol in pregnancy plasma, J. Lab. Clin. Med. **86:** 513, 1975.
6. Vaitukaitis, J. L., Braunstein, G. D., and Ross, T.: A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone, Am. J. Obstet. Gynecol. **113:** 751, 1973.
7. Buster, J. E., and Abraham, G. E.: Radioimmunoassay of plasma dehydroepiandrosterone sulphate, Ann. Lett. **5:** 543, 1972.
8. Kao, M., Voina, L., Nichols, A. N., and Horton, R.: Parallel radioimmunoassay for plasma cortisol and 11-deoxycortisol, Clin. Chem. **21:** 1644, 1975.
9. Townsley, J. D., Scheel, D. A., and Rubin, E. J.: Inhibition of steroid 3-sulfatase by endogenous steroids. A possible mechanism controlling placental estrogen synthesis from conjugated precursors. J. Clin. Endocrinol. Metab. **31:** 670, 1970.
10. Oakey, R. E., Cawood, M. L., and MacDonald, R. R.: Biochemical and clinical observations in a pregnancy with placental sulphatase and other enzyme deficiencies, Clin. Endocrinol. **3:** 131, 1974.
11. Goebelsmann, U.: A reliable method for the determination of urinary estriol in pregnancy, Clin. Chim. Acta **23:** 469, 1969.
12. France, J. T., and Liggins, G. C.: Placental sulfatase deficiency, J. Clin. Endocrinol. Metab. **29:** 138, 1969.
13. Cédard, L., Tchobrovsky, C., Guglielmina, R., and Mailhac, M.: Insuffisance oestrogenique paradoxal cours d'une gross essie normale par defaut de sulfatase, Bull. Fed. Soc. Gynecol. Obstet. Lang. Fr. **23:** 16, 1971.
14. France, J. T., Seddon, R. J., and Liggins, G. C.: A study of a pregnancy with low estrogen production due to placental sulfatase deficiency, J. Clin. Endocrinol. Metab. **36:** 1, 1973.
15. Tabei, T., and Henrichs, W. L.: Diagnosis of placental sulfatase deficiency, Am. J. Obstet. Gynecol. **124:** 409, 1976.
16. Roy, A. B.: Enzymological aspects of steroid conjugation, *in* Bernstein, S., and Solomon, S., editors: Chemical and Biological Aspects of Steroid Conjugation, New York, 1970, Springer-Verlag, pp. 74-130.

Fifth International Gender Dysphoria Symposium

The Gender Identity Clinic of Eastern Virginia Medical School will host the Fifth International Gender Dysphoria Symposium in Norfolk, Virginia, February 10-13, 1977. Presentations will be made in the areas of "Psychiatric Aspects of the Gender Dysphoria Syndrome," "Considerations of Male to Female and Female to Male Transsexuals," "Diagnostic Dilemmas and Treatment Failures," and "Follow-Up Studies." Additionally, guest speakers will address such topics as Therapeutic Guidelines, Legal and Social Problems, Nursing Aspects, and Theoretical Aspects of the Gender Dysphoria Syndrome. This continuing medical education program will be accredited by the American Medical Association and the associations of the various disciplines involved. All professionals are invited to attend. For registration information, contact: Terry Salasky, Coordinator, Gender Dysphoria Symposium, P. O. Box 1980, Norfolk, Virginia 23501.

Scalp abscess: A complication of the spiral fetal electrode

CRAIG A. WINKEL, M.D.
DONALD L. SNYDER, M.D.
JOHN B. SCHLAERTH, M.D.
San Francisco, California

During the period from September, 1974, to January, 1975, we performed 276 deliveries, of which 54 per cent were internally monitored with a spiral type of fetal electrode. Eight of the infants monitored (incidence, 5.4 per cent) developed scalp abscesses. We had had no previous complications associated with the electrodes. An intensive investigation was conducted to detect the causative factor(s) of the fetal scalp infections. Case histories of the mothers and infants were scrutinized, instruments were examined, the environment and techniques were analyzed. A survey of maternal and infant complications during the period from September, 1973, to August, 1974, served as control. The findings indicated that a different type of coil electrode had been substituted for the brand we had used previously. The new coil electrode had a barb at the tip, presumably to prevent its falling out of the scalp. We discontinued the use of the coil which had become suspect and returned to the type we had used previously. We have not had another incidence of fetal scalp infection associated with intrapartum monitoring.
(AM. J. OBSTET. GYNECOL. 126: 720, 1976.)

INTRAPARTUM fetal heart rate monitoring, a technique whereby an electrode is attached to the fetal scalp, is an accepted obstetric practice during the time the mother is in labor. Different types of electrodes have been devised. It was observed that the original clamp-on electrode could result in contusions and lacerations on the fetal scalp and, subsequently, a screw-on spiral type was designed. There have been reports of superficial scalp abscesses resulting from the use of both of these types of electrodes (incidence, 0.3 to 0.4 per cent).[1-3] One fetal death resulting from a severe infection beginning at the scalp electrode site has been reported.[4]

Since January, 1974, we have used the screw-on spiral type electrode for intrapartum fetal heart rate monitoring in 55 per cent of 394 patients in labor. We had no fetal scalp infections until September, 1974. During the next 5 months, we performed 276 deliveries, of which 54 per cent were internally monitored with a spiral type of fetal scalp electrode. Scalp abscesses developed in eight infants who had been monitored. Of these eight scalp infections, seven were severe but none was fatal. Four of the infections were caused by gram-negative rods; bacteroides species were isolated in two of the cases. Our incidence of infection associated with the fetal heart rate monitoring was 5.4 per cent during the epidemic period.

In January, 1975, an intensive investigation was instituted to find the causative factors of the epidemic. The electrode used for fetal heart rate monitoring became suspect. We immediately discontinued the use of that model and purchased the model we had used before the epidemic. We have had no further incidences of infant scalp abscesses or complications associated with the electrode.

From the Department of Obstetrics and Gynecology, Letterman Army Medical Center.

Presented at the Armed Forces District Meeting, American College of Obstetricians and Gynecologists, San Antonio, Texas, November, 1975.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Received for publication January 12, 1976.

Revised June 1, 1976.

Accepted June 18, 1976.

Reprint requests: Technical Publications Editor, Letterman Army Medical Center, Presidio of San Francisco, California 94129.

Table I. Maternal data

Pt.	Age* (yr.)	Duration of monitoring (hr./min.)	Method of membrane rupture duration (hr.)	Duration of labor		No. of vaginal examinations	Method of delivery	Episiotomy extension (degree)	Maternal morbidity
				Stage 1 (hr.)	Stage 2 (min.)				
1	24	11/ 0	Amniotomy (11)	19½	35	15	ELF	None	None
2	22	6/30	Amniotomy (8)	7†	180	9	Mid forceps rotation	Fourth	Endoparametritis (Bacteroides)
3	19	2/40	Leaking on admission (14)	7	40	6	Spontaneous	Fourth	None
4	24	10/ 0	Amniotomy (10)	16†	82	14	ELF	Fourth	None
5	22	7/ 0	Amniotomy (8)	15	94	10	ELF	Fourth	Endometritis (Bacteroides)
6	28	4/ 0	Amniotomy (4)	6‡	—	4	Cesarean section	None	Endometritis
7	26	8/15	Amniotomy (8)	8½	180	5	ELF	Fourth	Episiotomy infection *(Staph. aureus)*
8	21	11/ 0	Spontaneous at home (30)	17†	87	10	Spontaneous	Fourth	Amnionitis during labor

*All mothers were primigravidas except Patient No. 1, who was gravida 2. All mothers were para 0.
†Augmented by intravenous oxytocin (Pitocin).
‡One fetal scalp sample.

Table II. Infant data

Infant	Age at diagnosis (days)	Gram stain	Culture	Antibiotics	Surgical
1	14	Negative	Negative	Local	I & D*
2	7	Gram-negative rods	Bacteroides	Systemic	I & D
3	3	Negative	Negative	Local	None
4	2	Gram-positive cocci	Negative	Systemic	I & D
5	5	Gram-negative rods	Bacteroides	Systemic	I & D
6	2	Negative	Diphtheroids	Local	None
7	14	Gram-positive cocci	Staph. aureus	Systemic	I & D
8	14	Unknown	Unknown	Systemic	I & D†

*I & D = incision and drainage.
†Tip of fetal electrode was recovered from the abscess.

Methods and materials

The case histories of the mothers and the infants were scrutinized from all aspects. A survey of maternal complications for the period from September, 1973, to August, 1974, was made. These complications served as controls for the role of maternal infection, obstetric lacerations, maternal fever, infant trauma, antibiotic use, scalp sampling, and delivery methods. A survey of infant complications of the same period was made and served as control. The instruments were examined and the environment and techniques were analyzed.

Results

The maternal and infant data on the eight index cases are presented in Tables I and II. Investigation demonstrated no apparent differences in situation or technique for the control vs. survey periods. Primigravida births occurred with incidences of 52 and 49 per cent, respectively, in the control and index periods. Fourth-degree episiotomy extensions occurred in 8 per cent of control births and 11 per cent of survey births. Significantly, 75 per cent of the fourth-degree extensions in the controls and 67 per cent of those in the survey occurred in primigravida deliveries. Elective low forceps (ELF) were used 48 per cent of the time in the control period as opposed to 41 per cent of the survey.

As is noted, the incidence of maternal puerperal infection was 62.5 per cent in the index cases. An over-all incidence for control and survey periods varied between 8 and 11 per cent, respectively.

It was discovered that a different type of spiral electrode, produced by a different company, had been substituted by the purchasing department for the one

we had ordered and had been using previously (during the control period). This was done without professional knowledge or consultation. The factors apparently associated significantly with the newborn scalp abscesses were maternal puerperal infection, fourth-degree episiotomy extension (Table I), and the use of a new coil electrode (Table II).

Comment

Our incidence (5.4 per cent) of fetal scalp abscesses at the site of the electrode during the period from September, 1974, to January, 1975, was significantly higher than any percentage previously reported[1-3] and represented a complication we had not previously experienced in our department. McCrann and Schifrin[1] reported 20 documented cases of scalp abscesses in 5,000 monitored infants (incidence, 0.4 per cent). There was no correlation with the number of electrode applications, duration of monitoring, or concurrent amnionitis. Paul and Hon[2] reported on a series of over 4,000 monitored patients without serious fetal morbidity. They found an incidence of superficial scalp abscesses of 0.3 per cent. In 1971, Cordero and Hon[3] reported a series of 2,003 deliveries in which seven scalp abscesses (0.34 per cent) were seen. Recently, Turbeville and associates[4] reported a fetal death resulting from a severe infection beginning at the scalp electrode site. The electrode used in all these series was either the clamp-on type or the spiral from Corometrics Medical Systems.*

The eight infants in our series were delivered by the resident house staff; all were monitored with the Berkeley spiral electrode; one infant had a fetal scalp blood sample performed because of fetal distress, one was delivered by cesarean section, and five with forceps. Seven mothers were primigravidas, one was gravida 2; six of the eight had fourth-degree extensions of median episiotomies; four had postpartum febrile morbidity. Two of the patients with postpartum febrile courses had endometritis caused by bacteroides species.

The scalp abscesses were recognized as early as the second postdelivery day and as late as the fourteenth day. Gram stains of the material from the electrode site or from the exudate drained from the scalp abscesses were positive in four cases and cultures were positive in four cases. All the newborn infants had resolution of the infections without further complication after topical therapy or systemic antibiotics. Six of the eight cases had incision and drainage of the scalp abscesses (Table II).

On cursory inspection of the electrodes from the two companies,* we could see little difference. However, during our investigation, we closely inspected and compared these electrodes. The Berkeley electrode has a barb at the tip, presumably to prevent it from falling out after placement. In addition, the wire probe on the Berkeley electrode is thinner, is flat instead of round, and is 2 to 3 mm. longer than the Corometrics wire probe. These factors may permit the wire probe of the Berkeley electrode to straighten out when fully embedded in the fetal scalp and thus penetrate deeper into the tissues and possibly perforate the periosteum. At the time the electrode is removed from the infant's scalp, these characteristics enhance the possibility of injury and infection. In one case (infant No. 8), a tip of the electrode was retrieved at the time of debridement.

We have hypothesized that the barbed tip causes increased tissue trauma. Because of the increased stretch of the coil electrode when tension is applied, the trauma to the fetal tissue occurs deeper in the scalp. This tissue trauma may permit the proliferation of a small inoculum of anaerobic bacteria especially likely to occur when the episiotomy extends into the rectum. Since it appears that these scalp abscesses are slow in evolving, they may be easily overlooked during the first week of life.

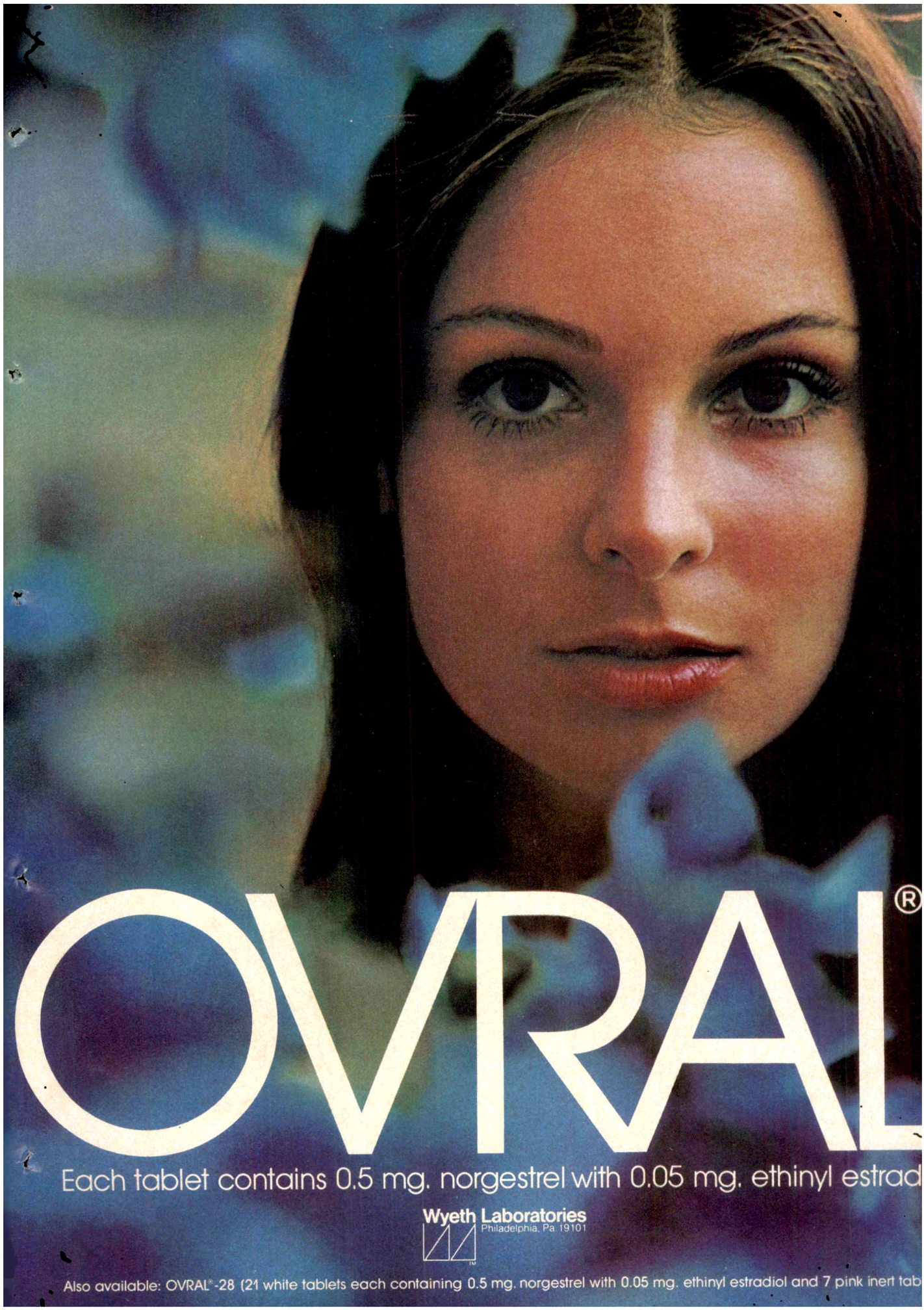
On the basis of findings which appear statistically significant, the use of the Berkeley spiral electrode was discontinued. We began again to use the electrode from Corometrics Medical Systems. We have had no fetal scalp infections in 552 deliveries, 57 per cent of which were monitored using the spiral fetal scalp electrode.

*Corometrics Medical Systems, 200 Barnes, Industrial Park, Wallinford, Connecticut 06492.

*Berkeley Bio-engineering, 600 McCormick St., San Leandro, California 94577; Corometrics Medical Systems, 200 Barnes, Industrial Park, Wallinford, Connecticut 06492.

REFERENCES

1. McCrann, D. J., Jr., and Schifrin, B. S.: Fetal monitoring in high risk pregnancy, Clin. Perinatol. **1:** 226, 1974.
2. Paul, R. H., and Hon, E. H.: Clinical fetal monitoring. IV. Experience with a spiral electrode, Obstet. Gynecol. **41:** 777, 1973.
3. Cordero, L., and Hon, E. H.: Scalp abscess. A rare complication of fetal monitoring, Pediatrics **78:** 533, 1971.
4. Turbeville, D. F., Heath Jr., R. E., Bowen Jr., F. W., and Killiam, A. P.: Complications of fetal scalp electrodes: A case report, Am. J. Obstet. Gynecol. **122:** 530, 1975.


OVRAL®
Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estrad
Wyeth Laboratories
Philadelphia, Pa. 19101
Also available: OVRAL®-28 (21 white tablets each containing 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol and 7 pink inert tab



Estrogen as natural to her body as the estrone it restores

OGEN®
(PIPERAZINE ESTRONE SULFATE)

Helps you arrive at the minimum estrogen dosage needed to relieve her symptoms



One Divide-Tab® tablet may well be the correct dosage but only trial can tell.



Some patients may require only half this dosage for relief of symptoms.



Other patients may experience partial relief of symptoms when a half-tablet more would provide complete control.

In short: Divide-Tab tablets help you determine how much is needed and how little is enough . . . with one prescription.

6053143

See following page for Brief Summary.

ABBOTT

OGEN® PIPERAZINE ESTRONE SULFATE

offers you four Divide-Tab® dosage strengths for greater flexibility



OGEN .625
(piperazine estrone sulfate 0.75 mg., calculated as sodium estrone sulfate 0.625 mg.)



OGEN 1.25
(piperazine estrone sulfate 1.5 mg., calculated as sodium estrone sulfate 1.25 mg.)



OGEN 2.5
(piperazine estrone sulfate 3 mg., calculated as sodium estrone sulfate 2.5 mg.)



OGEN 5
(piperazine estrone sulfate 6 mg., calculated as sodium estrone sulfate 5 mg.)

6053143R1

Brief Summary

Important Notes: It has now been conclusively established that the use of oral contraceptives containing estrogens and progestins is associated with an increased risk of thromboembolic disease. Retrospective studies have shown a statistically significant association between the use of these drugs and thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism. This conclusion is based on three principal studies[1-3] done in Great Britain and one[4] done in the U.S. Based on these studies it has been estimated that users of oral contraceptives are four to seven times more likely than nonusers to develop thromboembolic disease with no evident cause. The American study also indicated that the increased risk did not persist after the drug was discontinued, nor was it enhanced by long-term administration. Although this study was not designed to evaluate a difference between products, the results suggested that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis[5] of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen in the oral contraceptive used. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles to use the smallest effective dose of estrogen in treating patients, whenever feasible.

The degree of risk associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate has not yet been satisfactorily determined.

Long-term administration of both natural and synthetic estrogens in multiples of the human dose to subprimate animal species increases the frequency of some animal carcinomas. Conclusions based on these data cannot be applied directly to man. The possible carcinogenicity of the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued.

It has been reported in a recent study[6] done in the United States that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of the development of vaginal adenocarcinoma years later in the exposed offspring.

Indications: OGEN (piperazine estrone sulfate tablets) is indicated:—For replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure. In the management of senile vaginitis; in kraurosis vulvae with or without pruritus.

For the prevention of postpartum breast engorgement.

In the management of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

In inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: Estrogens are contraindicated in patients with known or suspected carcinoma of the breast, except in those cases of progressive disease not amenable to surgery or irradiation occurring in women who are at least five years postmenopausal or in men in whom castration is not feasible. They are also contraindicated in patients with other known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium.

These drugs are further contraindicated in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions, in patients with markedly impaired liver function, and in those with undiagnosed, abnormal genital bleeding.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected, the drug should be discontinued immediately. If there is a sudden onset of proptosis, diplopia, or migraine, the medication should be discontinued pending an examination. If papilledema or retinal vascular lesions are found, the medication should be withdrawn.

Estrogens may be excreted in the mother's milk, and an estrogenic effect upon the nursing infant has been described. The long range effect on the infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This effect is not dependent on dose or immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Precautions: Because normal endogenous hormone production varies among individuals, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, or other effects (see ADVERSE REACTIONS).

Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

If any unexplained or excessive vaginal bleeding occurs during estrogen therapy, nonfunctional causes should be considered. The drug should be discontinued and a thorough investigation made of the cause, being certain to ascertain that a malignancy is not present.

Pre-existing uterine fibromyomata may increase in size with estrogen therapy; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

A pre-treatment physical examination should include special attention to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. Estrogens should be used cautiously in women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast.

To avoid this, oral estrogens should be administered cyclically to the menopausal or hypogonadal patient.

Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Estrogens influence the metabolism of calcium and phosphorus and should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is not complete. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Urinary stress incontinence may occur when large doses of estrogens are used in nonpregnant women.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient receiving an estrogen, it is recommended that they be repeated after the drug has been withheld for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function will require further study.

Adverse Reactions: Although not all of the following reactions have been specifically associated with OGEN (piperazine estrone sulfate tablets), they have been reported with estrogens generally and may be encountered when giving any estrogen.

Gastrointestinal: nausea, anorexia, vomiting, abdominal cramps, bloating, cholestatic jaundice and increase or decrease in body weight.

Genitourinary: sodium and water retention, breakthrough bleeding, spotting, and withdrawal bleeding, increased cervical mucus, reactivation of endometriosis, and cystitis-like syndrome.

Endocrine: breast swelling and tenderness, possible diminution of lactation when given immediately postpartum, increased blood sugar levels, and decreased glucose tolerance.

Central Nervous System: headaches, mental depression, increase or decrease of libido, nervousness, dizziness, fatigue irritability and malaise.

Dermatologic-Hypersensitivity: loss of scalp hair, allergic reactions and rashes, hemorrhagic eruption, itching, erythema nodosum, and erythema multiforme.

Musculoskeletal: backache.

Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches.

Hematologic: a statistically significant association has been demonstrated between the use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuroocular lesions (e.g., retinal thrombosis and optic neuritis).

Miscellaneous: premenstrual-like syndrome and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

ABBOTT

MOSBY
TIMES MIRROR

Announcing...
the first definitive
investigation
of human andrology

ANNOUNCING...

A new book!

HUMAN SEMEN AND FERTILITY REGULATION IN MEN

This first major reference in the field examines andrology as a vital entity of human reproduction. More than 90 internationally-known authorities from leading andrology institutes in Europe and Australia provide you with research material never before available. You'll find insightful discussions on: behavioral aspects of sexual inadequacy; basic science and clinical components — anatomy, physiology, biochemistry, and immunology; fertility regulation; male contraception; artificial insemination; vasectomy; and much more. Make andrology a successful aspect of your practice with this dynamic new book!

Edited by E.S.E. Hafez, Ph.D.; with 97 contributors. September, 1976. 616 pages plus FM I-XVIII, 7¼" × 10½", 559 illustrations. Price, $47.50.

ORDER BY PHONE!
Call (800) 325-4177 ext. 10. In Missouri call collect — (314) 872-8370 ext. 10. 9 am to 5 pm (CST). Monday through Friday.

MOSBY
TIMES MIRROR

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

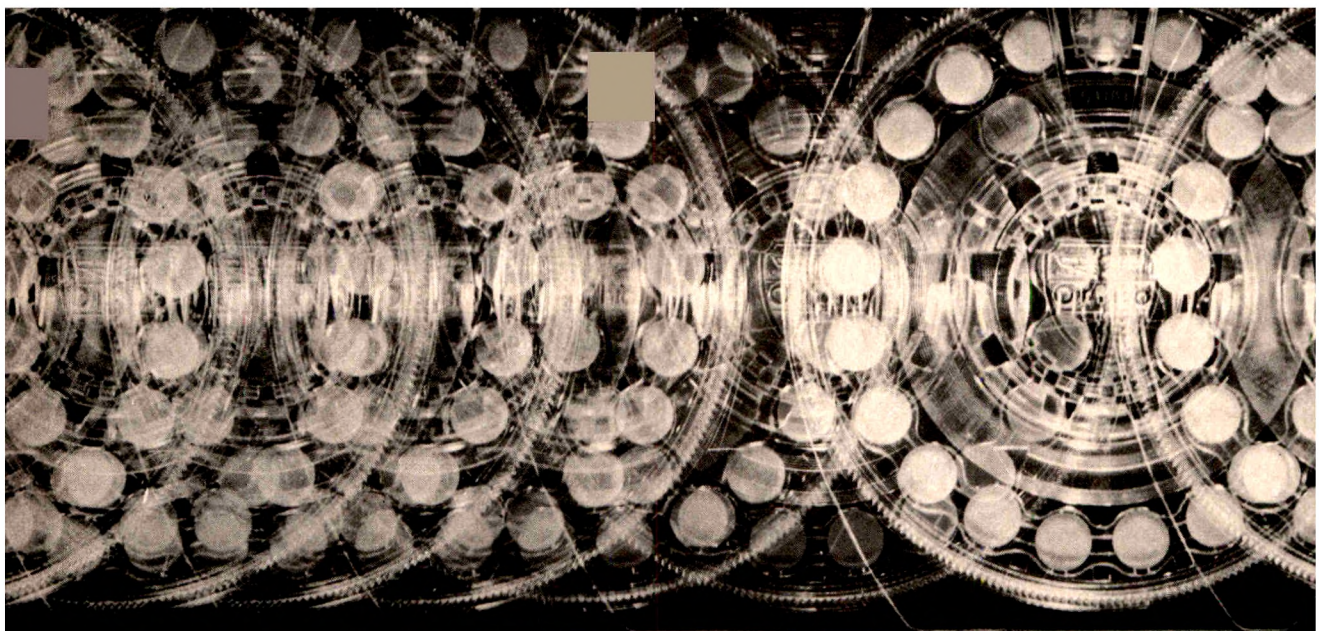
Community Hospital will sponsor first year of private, solo practice for OB-GYN. Prefer someone finishing Residency in June, 1977. Guaranteed income, paid move, malpractice insurance paid and rent-free office and equipment. Please include C. V. Reply Box AJOG-3.

ASSISTANT DIRECTOR OF NURSING

Perinatal

Strong, creative, well qualified assistant director of nursing for established expanding perinatal center. Responsible for quality of nursing practice and coordination among a variety of maternal and neonatal outpatient clinics, birth room and recovery room, post partum, well baby and admissions nursery and special care nursery, which includes intensive care, growing up and intermediate nurseries. Large high-risk population. Active participation in interdisciplinary and community planning expected. Master's degree in clinical area required. Demonstrated competence in organization and administration as well as depth knowledge in obstetrical nursing practice. Send comprehensive resume to: Greta Fraser, Director of Nursing Service, MADISON GENERAL HOSPITAL, 202 South Park Street, Madison, WI. 53715, or call collect: (608) 267-6015.

An Equal Opportunity Employer.

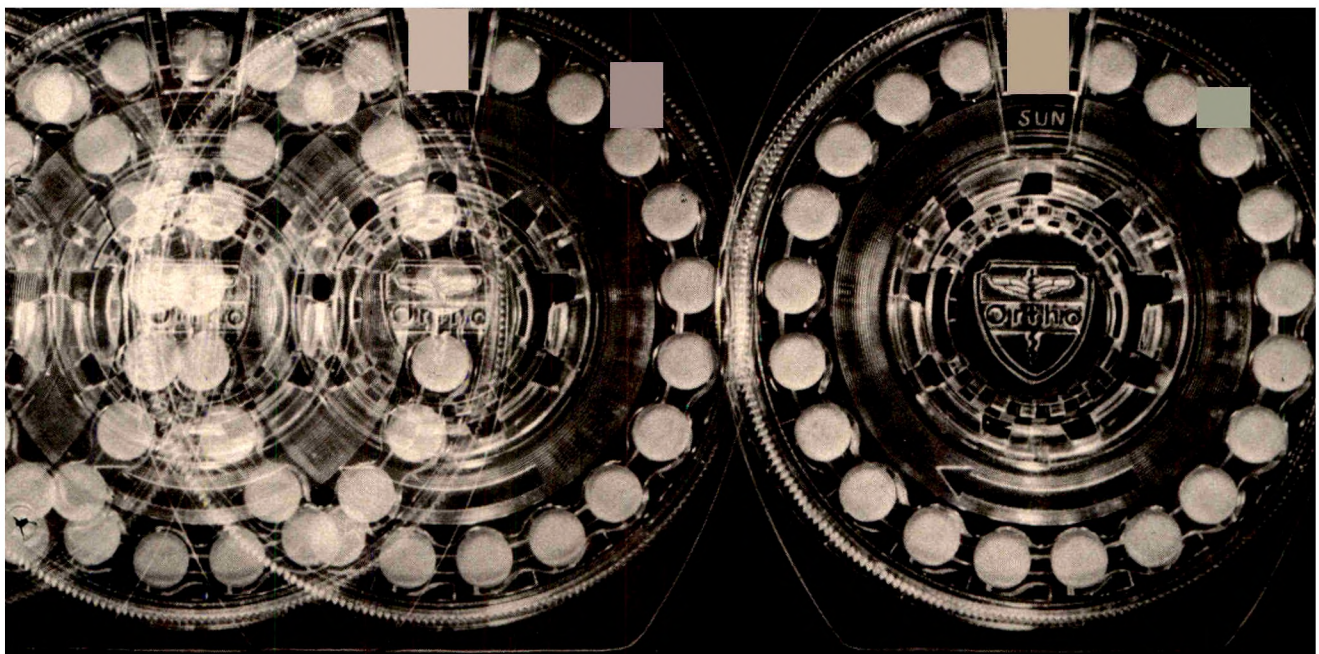


ModiCon

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.
In the 28-day regimen, each green tablet contains inert ingredients.

to offer lower-dose oral contraception with higher-dose effectiven

© Ortho Pharmaceutical Corporation, 1976



is back.

Reformulated without dye *ModiCon is back, but without the coloring agent. Quality control testing on new white ModiCon demonstrates excellent stability.*

No change in hormonal content *Alterations in the hormonal content were not necessary. ModiCon still contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.*

Same clinical benefits *ModiCon is back in a new white tablet to offer the same clinically documented benefits as before: low hormonal intake – highly effective – well tolerated† – and the only lower-dose combination available in the unique DIALPAK* Tablet Dispenser.*

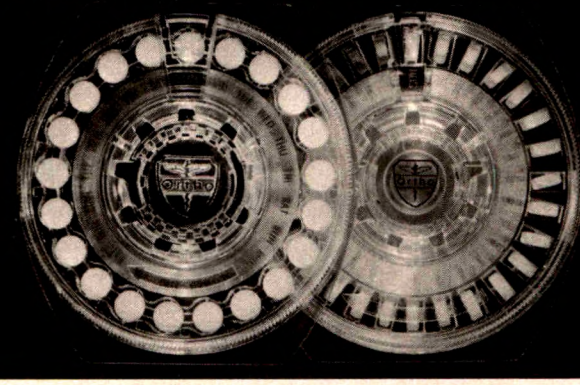
Two regimens *Available in both 21 and 28-day regimens.*

†It should be noted that pregnancy rates are usually derived from studies conducted by different investigators in several population groups and they cannot be compared with precision.

‡Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

ModiCon TRADEMARK is back.

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.



In both 21 and 28-day regimens

Description: Each MODICON Tablet contains 0.5 mg of the progestational substance, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

Each green tablet in the 28-day regimen contains inert ingredients.

Actions: MODICON acts through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of MODICON.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with MODICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of MODICON in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with MODICON. Therefore, if such tests are abnormal in a patient taking MODICON, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged MODICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving MODICON therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with MODICON may mask the onset of the climacteric. 10. The pathologist should be advised of MODICON therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steriods. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, MODICON should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during MODICON therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J Coll Gen Pract *13*:267-279, May 1967. **2.** Inman, W.H.W.; Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Br Med J *2*:193-199, April 27, 1968. **3.** Vessey, M.P.; Doll, R.: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Br Med J *2*:651-657, June 14, 1969. **4.** Sartwell, P.E.; Masi, A.T.; Arthes, F.G.; Greene, G.R.; Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Am J Epidemiol *90*:365-380, Nov. 1969. **5.** Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis, N Engl J Med *288*(17):871-878, April 26, 1973. **6.** Oral Contraceptives and Stroke in Young Women. Associated Risk Factors, J.A.M.A. *231*(7):718-722, Feb. 17, 1975. **7.** Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall-Bladder Disease, and Breast Tumours. Report from the Boston Collaborative Drug Surveillance Programme, Lancet: 1399-1404, June 23, 1973. **8.** Royal College of General Practitioners: Oral Contraceptives and Health: 1-100, May 1974. **9.** Vessey, M.P.; Doll, R.; Fairbairn, A.S.; Glober, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives, Br Med J *3*:123-126, July 18, 1970. **10.** Greene, G.R.; Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection, Am J Public Health *62*(5):680-685, May 1972. **11.** Mann, J.L.; Vessey, M.P.; Thorogood, M.; Doll, R.: Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice, Br Med J *2*:241-245, May 3, 1975. **12.** Mann, J.L.; Inman, W.H.W.: Oral Contraceptives and Death from Myocardial Infarction, Br Med J *2*:245-248, May 3, 1975. **13.** Nora, J.J.; Nora, A.H.: Birth Defects and Oral Contraceptives, Lancet: 941-942, April 28, 1973. **14.** Janerich, D.T.; Piper, J.M.; Glebatis, D.M.: Oral Contraceptives and Congenital Limb-Reduction Defects, N Engl J Med *291* (14):697-700, Oct. 3, 1974.

3/76

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and six references. Illustrations or additional references require a proportionate reduction in total words.

Adverse effect of amniofetography on fetal thyroid function

F. RODESCH, M.D., PH.D.
M. CAMUS, PH.D.
A. M. ERMANS, M.D., PH.D.
J. DODION, M.D.
F. DELANGE, M.D., PH.D.
Brussels, Belgium

Amniofetography is a valuable tool for the diagnosis of fetal malformations. This technique is being used routinely in pregnancies carrying a high risk of external fetal malformations. There are very few published data concerning the effect of radiopaque dyes, containing large amounts of iodide, on fetal thyroid function. We have performed serial determinations of serum thyrotropin and thyroxine in seven newborn infants to assess the effect of amniofetography on fetal thyroid function. This work demonstrates that amniofetography induces a transient impairment of fetal thyroid function. (AM. J. OBSTET. GYNECOL. 126: 723, 1976.)

AMNIOGRAPHY OUTLINES radiographically the amniotic cavity and allows visualization of the fetal gastrointestinal tract. Fetography makes use of the affinity of a fat-soluble contrast medium for vernix caseosa, providing a clear-cut outline of fetal soft tissue. Amniofetography (AFG), in which a combined injection of a water- and a fat-soluble radiopaque dye is used, is clearly a valuable tool for the diagnosis of fetal malformations. Today AFG is commonly performed in pregnancies carrying a high risk of external fetal malformations.

It is well established that protracted treatment with iodides can lead to thyroid enlargement and goiter in adults and children. Cases of congenital goiter subsequent to chronic intake of large amounts of iodine by

From the Department of Obstetrics and Gynecology, Human Reproduction Research Unit, Interdisciplinary Institute for Research in Human and Nuclear Biology, and the Departments of Radioisotopes and Pediatrics, Hôpital Saint-Pierre, Free University of Brussels.

Supported by "Fonds de la Recherche Scientifique Médicale" (Belgium) and by a contract from the Ministère de la Politique Scientifique (Belgium) within the framework of the Association Euratom–University of Brussels–University of Pisa.

Reprint requests: Dr. F. Rodesch, Department of Gynecology and Obstetrics, Hôpital Saint-Pierre, Rue Haute, 322-1000 Brussels, Belgium.

Table I. Serum T_4 and TSH concentrations in cord blood and at the fifth day of life

Case No.	Time of injection prior to delivery (days)	Cord blood		Fifth day	
		TSH (μU/ml.)	T_4 (μg/100 ml.)	TSH (μU/ml.)	T_4 (μg/100 ml.)
1	<1	–	–	7.0	–
2	<1	9.9	7.2	27.0*	–
3	2.0	3.5	11.1	51.0*	7.5
4	2.5	–	–	36.5*	–
5	5.0	31.5*	8.4	49.0*	–
6	5.0	>50*	16.5	50.0*	11.4
7	13.0	51.0*	7.2	51.0*	5.1*

*Abnormal results according to the studies of Delange and associates[3] for TSH and of Fisher and Sack[6] for T_4.

the mother have also been well documented.[1] However, there are very few published data[2] relative to the effects on the fetal thyroid of radiopaque contrast dyes injected into the amniotic cavity. Both the water- and lipid-soluble dyes used in AFG contain large amounts of iodide.

The aim of this study was to assess the effect of AFG on the fetal thyroid. Thyroid function of the newborn infant was evaluated by serial determinations of serum thyroxine (T_4) and thyrotropin (TSH). Our data demonstrate an adverse effect of AFG on neonatal thyroid function. This risk of transient hypothyroidism should be considered as a strong deterrent against unnecessary AFG.

Methods

AFG. The site selected for amniocentesis was the space occupied by the fetal arms and legs. Amniocentesis was performed with the use of local anesthesia. The needle tip entered the amniotic cavity with the stylet in place, and placement was verified by the ease of removal of amniotic fluid. A catheter was then introduced through the needle, and the needle was removed. The contrast materials were injected through the catheter. For the purpose of fetal delineation, 12 ml. of iodized ethyl esters of the fatty acids of poppy seed oil* was used. In all cases, 30 ml. of a water-soluble contrast medium (meglumine diatrizoate†) was injected simultaneously. Two roentgenograms were obtained 24 hours after the injection.

Data on seven AFG's are reported. The indication for the procedure was a high risk of fetal malformation: polyhydramnios (four cases) and severe intrauterine growth retardation (three cases). No fetal malformations were observed on roentgenograms; this was confirmed by clinical examination of the newborn infants. None of the seven pregnant women had any symptoms of thyroid disease or any evidence of thyroid enlargement on clinical examination. Moreover, the serum T_4 and TSH levels confirmed the euthyroid state.

Assessment of thyroid function in the newborn infant. Systematic screening for congenital hypothyroidism has been performed by our maternity service since July, 1974. The method used has been described in detail elsewhere.[3] Serum TSH has been measured on the fifth day with the use of the TSH Phadepas kit.* The mean level (± standard error) for 901 patients is 1.7 ± 1.0 μU per milliliter; 12 μU per milliliter was considered the upper limit of normal as the results were below this value in 99.2 per cent of the cases. Newborn infants with a serum TSH level above the "critical" value underwent control investigations. Serum T_4 was determined according to the method of Murphy and Pattee.[4] In the present investigation, the serum TSH concentration was measured systematically on the fifth day with simultaneous T_4 determinations in four cases. In five cases, serum T_4 and TSH were determined in cord blood.

Results

Table I shows the results of serum T_4 and TSH measurements in the seven neonates at birth and at the fifth day of life. The cases are classified according to the increase in time interval between AFG and delivery. The most striking observation is that six of seven infants exhibited a very high TSH level at the fifth day of life, ranging from 27.0 to 51.0 μU per milliliter, i.e., markedly above the upper limit of 12 μU per milliliter. Cord T_4 and TSH concentrations were normal in two cases, but cord TSH was increased in three other subjects (Nos. 5, 6, and 7). It should be pointed out that this situation was observed only when the delay between AFG and birth was at least five days. Moreover, an abnormally low serum T_4 concentration at the fifth day was observed only in the patient with the longest delay, i.e., 13 days.

Table II summarizes the results of the follow-up examinations. In three cases (Nos. 4, 5, and 7), TSH had reverted to normal, and the results of other follow-up examinations were also normal. However, in two cases (Nos. 3 and 6), TSH was still markedly increased and T_4 was decreased. In Case No. 6, a

*Lipiodol F.
†Angiografin.

*Pharmacia AB, Uppsala, Sweden.

Table II. Results of the follow-up examinations in the seven cases

Case No.	*TSH (μU/ml., fifth day)*	*Follow-up*				
		Day	*TSH (μU/ml.)*	*T_4 (μg/100 ml.)*	*Clinical findings*	*Period of therapy*
1	7.0	8	–	9.7	None	–
2	27.0*	9	14.7*	14.6	Apathy and jaundice	Days 13 to 36
3	51.0*	19	51.0*	4.3*	None	Days 22 to 54
4	36.5*	17	5.8	7.0	None	–
5	49.0*	38	1.9	13.5	None	–
6	50.0*	16	>250*	3.1*	Goiter	Days 23 to 39
7	51.0*	17	3.9	6.6	None	–

*Abnormal results according to the studies of Delange and associates[3] for TSH and of Fisher and Sack[6] for T_4.

palpable goiter was confirmed by scintigraphy. In Case No. 2, serum TSH was moderately increased (14.7 μU per milliliter) and T_4 was normal. Nevertheless, the infant exhibited an episode of jaundice and apathy compatible with hypothyroidism. These three patients (Nos. 3, 6, and 2) received thyroid extracts for two to four weeks.

Comment

The present work shows that AFG impairs thyroid function of the newborn infant and may result in congenital hypothyroidism. Of the seven newborn infants in our series, six exhibited strikingly increased serum TSH levels at the fifth day of life. Follow-up examinations performed in the next few days clearly confirmed the diagnosis of hypothyroidism in two cases (Nos. 3 and 6) by the association of an increased TSH level and a decreased T_4 level. Thyroid failure could be strongly suspected in a third case (No. 2), despite a normal T_4 value, on the basis of increased TSH and clinical symptoms (apathy and unexplained jaundice) which disappeared immediately after thyroid hormone treatment. In the three other cases (Nos. 4, 5, and 7), TSH and T_4 concentrations had reverted to normal at the time of follow-up. Furthermore, impairment of thyroid function was suspected even at birth in three cases on the basis of increased TSH levels in the cord blood. The precocity of the appearance of the biochemical abnormalities seemed to be correlated with the time delay between AFG and delivery.

The results of the follow-up examinations of the patients have shown a rapid clinical and biochemical normalization either spontaneously or after a short period of treatment with thyroid extracts. This indicates that impairment of thyroid function in the newborn infant after AFG is transient. Nevertheless, due to the vulnerability of the human brain in the perinatal period, even silent and transient hypothyroidism must be diagnosed and treated promptly in order to avoid any cerebral damage.[5]

The mechanism responsible for thyroid impairment is most probably, as in congenital iodide goiter, via a toxic effect of iodide on intrathyroidal hormonogenesis (Wolff-Chaikoff effect[2]) which accounts for the delay between AFG and TSH elevation and for the transient character of the thyroid dysfunction. This interpretation is supported by the fact that the urinary concentration of iodide in one newborn infant was 900 μg per 100 ml. at birth and in another was 230 μg per 100 ml. at one month, about 80 to 2,000 times higher than normal in Belgium.

Our conclusions are in disagreement with those of Morrison and associates.[2] These authors concluded that AFG has no adverse effects on thyroid function on the basis of normal serum T_4 levels and triiodothyronine resin uptake in the first day of life. They did not measure serum TSH levels, which are definitely better for detecting slight thyroid impairment.[6] It is also very important to point out that Morrison and associates used only a water-soluble contrast medium (meglumine diatrizoate*). These authors explained the absence of perturbation of thyroid function by the fact that, as shown by their chromatographic studies of amniotic fluid aliquots, the iodine remained organically bound until it was eliminated from the amniotic compartment within two or four days after injection.

It is unnecessary to emphasize the potential uses of outlining the fetus radiographically, as AFG is now being used universally. The contribution of this paper is to underline the necessity of systematically and carefully evaluating the thyroid function of these newborn infants in order to be able to correct immediately any thyroid disturbance.

*Renografin-60.

REFERENCES

1. Vagenakis, A. G., and Braverman, L. E.: Adverse effects of iodides on thyroid function, Med. Clin. North Am. **59:** 1075, 1975.
2. Morrison, J. C., Boyd, M., Friedman, B. I., Bucovaz, E. T., Whybrew, W. D., Koury, D. N., Wiser, W. L., and Stewart, A. F.: The effects of Renografin-60 on the fetal thyroid, Obstet. Gynecol. **42:** 99, 1973.
3. Delange, F., Camus, M., Winkler, M., Dodion, J., and Ermans, A. M.: Serum thyrotropin determination at the fifth day of life as a screening procedure for congenital hypothyroidism, Arch. Dis. Child. In press.
4. Murphy, B. E. P., and Pattee, C. J.: Determination of thyroxine utilizing the property of protein-binding, J. Clin. Endocrinol. Metab. **24:** 187, 1964.
5. Barnes, N. D.: Serum TSH measurement in children with thyroid disorders, Arch. Dis. Child. **50:** 497, 1975.
6. Fisher, D. A., and Sack, J.: Thyroid function in the neonate and possible approaches to newborn screening for hypothyroidism, *In* Fisher, D. A., and Burrow, G. N., editors: Perinatal Thyroid Physiology and Disease, Kroc Foundation Series No. 3, New York, 1975, Raven Press, p. 197.

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

A simple, rapid procedure for the laboratory diagnosis of early pregnancies

MAURICE HAROLD FRIEDMAN AND MAXWELL EDWARD LAPHAM

American Journal of Obstetrics and Gynecology, vol. 21, pp. 405-410, 1931

Of course, there is also the disadvantage of toxicity in a small percentage of urines. This is quite as true of the Zondek-Aschheim procedure. With our method, we found 3 of 112 specimens too toxic to yield satisfactory results. Zondek reports that about 6 per cent[12] of the samples submitted were too toxic to be handled, and to obviate this difficulty, he has devised a method by which these toxic urines may be made innocuous. Since the appearance of this paper we have not encountered a sample with which to test his procedure.

Compared with the minor disadvantages of the use of the rabbit as we have proposed, are several real advantages. In the first place, the test as we have used it may be completed in forty-eight hours, as contrasted with one hundred hours for the performance of the original Zondek-Aschheim test. In an effort to decrease the time necessary for the performance of a test, Zondek proposes a method[11] of concentrating the active substances in the urines of pregnant women so that the test may be completed in about fifty hours. With this modified



Fig. 1.—A typical positive reaction showing the corpora hemorrhagica produced by the injections of urine from a pregnant woman.

technic, however, only positive reactions are significant. Really, if one were in a hurry, he could use two or more rabbits and sacrifice one or more of the animals eighteen hours after the first injection. In a large number of animals the ovarian changes will have occurred by this time, for, as reported previously,[3] even a single intravenous injection of urine from a pregnant woman can provoke ovulation in a rabbit within twelve to fourteen hours. Before the present routine was adopted, we did use the single intravenous dosage with the eighteen-hour autopsy, but found that it was not entirely reliable. Yet, in the event of necessity, this method could be employed, if one would not place too much faith in negative results. By this means crude urine may be used, thus avoiding the need of alcoholic precipitation and subsequent concentration of the active substances.

Another advantage of the method we propose is the ease with which the results can be determined. When the mouse is used as the test animal, a hand lens is needed frequently to determine the presence or absence of a positive reaction, and in about 12 per cent of the cases, microscopic study is required.[12] When the rabbit is used, the results

The hormonal diagnosis of pregnancy was facilitated greatly by Friedman and Lapham's modification of the Aschheim-Zondek (A-Z) test (Klin. Wochenschr. 7: 8, 1404 and 1453, 1928). It was particularly useful because it overcame several problems of the A-Z test, namely, the difficulty of maintaining immature mice of the proper weight, the requirement of six injections, and the long time interval (100 hours) required before the result was known. In contrast, the Friedman test required two or three injections into a mature female rabbit, and the answer was available in 24 to 72 hours. In a positive test, the rabbit ovaries showed fresh corpora lutea or corpora hemorrhagica (see the illustration). In this paper, the authors reported that in 92 patients the results of the test agreed correctly with the ultimate clinical diagnosis. A positive result usually was obtained 17 days following conception and remained so throughout pregnancy. The technique of the original test was modified later to a single injection of 10 ml. of morning urine with the rabbit ovaries inspected in 24 to 48 hours. The Friedman test was used for several decades as the most sensitive and reliable method of diagnosing pregnancy and neoplasms containing chorionic tissue.

The development of the rabbit test for pregnancy

MAURICE H. FRIEDMAN, PH.D., M.D.
La Jolla, California

THE DEVELOPMENT OF the pregnancy test was actually something of an accident—something I had not been seeking purposely. My attention had been drawn some years earlier to the peculiar and special mechanism of ovulation in the rabbit, which, like the revolutionary soldier, had been conditioned not to "fire until you can see the whites of their eyes," in this special case, the eyes of the male rabbit. The fact that the rabbit had an almost constant supply of ripe ovarian follicles but did not discharge them until some hours after coitus had led most scholars of that time[6] to believe that the mechanism was entirely neural, i.e., that the act of coitus resulted in some stimulation of nerves to the ovaries which caused the discharge of the ripe follicles.

It seemed to me that a reflex which required some ten or more hours for completion was a most unusual—and improbable—nervous system response, and I was determined to investigate this.

As soon as Dr. Anton Carlson shipped me off to the Department of Physiology, University of Pennsylvania (without telling me that he had been there once earlier in his career and could not stand it), I started my experiments on the mechanism of ovulation in the rabbit. By the end of 1928, it was clear to me that some humoral mechanism was involved since rabbit ovulation occurs in transplanted ovaries, in which the nerves are not intact.[3, 4] To further the solution of this problem, I searched for a source of suitable hormones which could provoke ovulation in the unmated rabbit. I really wanted to use hog pituitaries, but, because of the poverty of the University of Pennsylvania and my greatly restricted research funds, I was forced to seek some other material. About that time, I read of the reports of Aschheim and Zondek,[1, 7] indicating that the urine of pregnant women contained some substance or substances resembling pituitary hormones. I must confess that at first I was skeptical of this report, because at that time some bizarre claims were being made in the European literature. Nevertheless, I had little choice in the matter, and the Obstetrical Division of the Hospital and my very good friend Max Lapham, a resident in Obstetrics, were next door.

When the first results appeared, it was obvious that the rabbit responded with spectacular regularity to the injection of urine of pregnancy, and this animal had many great practical advantages over the mouse or rat for this purpose. I[2] first reported the use of urine from pregnant women as a hormonal test for pregnancy the following year. The necessary material was quickly assembled, and I sent the paper on the Pregnancy Test to Morris Fishbein for publication in the *Journal of the American Medical Association.* This was in either late 1929 or very early 1930. Dr. Fishbein did not comment on the paper but continued to hold it month after month without any action. After a long waiting period, I wrote insisting that he either accept the paper for publication or return it—which he did eventually, saying that it was unsuitable for publication in the *Journal of the American Medical Association.* After this, I delivered the manuscript to Dr. Joseph Bolivar De Lee in Chicago, who facilitated its publication in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.[5]

The original version of the pregnancy test relied on multiple injections for a short period with inspection of the rabbit ovaries 48 hours after the initial injection. I personally did not try any other method, having demonstrated that the above technique was sufficiently accurate and prompt for clinical use. Knowing the great variations in the sensitivity of rabbits to gonadotropic stimulation, I did not wish to jeopardize the accuracy of the test by decreasing either the number of injections or the time during which they were made. You can better appreciate this by looking at my subsequent papers on quantitative aspects of this question.

The test had a good reception because of its practicality, but, in fact, it was only a modification of the fundamental Aschheim-Zondek test and, therefore, not a significant discovery. Zondek was very gracious in his reaction to my publication and we became close friends. In the postwar years, his publications from Holland and later from Jerusalem revealed what a great scholar and scientist he was.

This article was received from Dr. Friedman in response to a query concerning the development and introduction of the Friedman test for pregnancy.

REFERENCES

1. Aschheim, S., and Zondek, B.: Schwangerschaftsdiagnose aus dem Harn (durch Hormonnachweis), Klin. Wochenschr. **7:** 8, 1404, 1453, 1928.
2. Friedman, M. H.: Effect of injections of urine from pregnant women on ovary of the rabbit, Proc. Soc. Exp. Biol. Med. **26:** 720, 1929.
3. Friedman, M. H.: The mechanism of ovulation in the rabbit. I. The demonstration of a humoral mechanism, Am. J. Physiol. **89:** 438, 1929.
4. Friedman, M. H.: Humoral mechanisms concerned in ovulation in the rabbit, Endocrinology **14:** 328, 1930.
5. Friedman, M. H., and Lapham, M. E.: A simple, rapid procedure for the laboratory diagnosis of early pregnancies, AM. J. OBSTET. GYNECOL. **21:** 405, 1932.
6. Marshall, F. H. A.: The physiology of reproduction, ed. 2, London, 1922 Longmans, Green & Company, p. 561.
7. Zondek, B., and Aschheim, S.: Das hormon des hypophysenvorder-Lappens. I. Testobjekt zum Nachweis des Hormons, Klin. Wochenschr. **6:** 248, 1927.

COMMUNICATIONS IN BRIEF

This section is suitable for reporting cases, results of therapeutic trials, and descriptions of new procedures or instruments. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

The effect of promethazine hydrochloride on fetal and maternal lymphocytes

JOHN P. GUSDON, JR., M.D.
GLENN A. HERBST, M.A.

Department of Obstetrics and Gynecology, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina

THIS LABORATORY has been involved in the study of promethazine hydrochloride and its use in erythroblastosis for many years. Our interest in this drug was originally aroused by the report by Bierme-Alie-Enjalbert[1] of a possible amelioration of the effects of erythroblastosis in 11 patients treated with that drug during pregnancy. The possibility that its ability to ameliorate this immunologically mediated disease by an immunosuppressive capability was studied by us in patients and in the laboratory. Our most recent publication reviews our prior work and documents the in vitro inhibition, by promethazine hydrochloride, of the ability of macrophages of the newborn infant to form rosettes with anti-D opsonized red blood cells.[2] We have previously shown that fetal red blood cell destruction in erythroblastosis caused by the Rh antigen was not accomplished directly by the antibody and that the anti-D was not complement-fixing. In addition, we have also documented the ability of promethazine hydrochloride to inhibit lymphocyte-mediated functions in vivo in animals. The first paper we published concerning the effectiveness of promethazine hydrochloride in the treatment of erythroblastosis involved only 15 patients. A subsequent paper involving more than 40 patients is in preparation. However, we have maintained a concern regarding the effects which promethazine hydrochloride might have on the mother and child. The action of promethazine hydrochloride in ameliorating the effects of erythroblatosis is probably not solely due to its immunosuppressive activities. However, the documented immunosuppressive activity of this drug engenders some concern over the long-term effects of administration of such a drug to both the mother and fetus. Therefore, we have studied some aspects of immunologic function in both the mother and baby at the time of birth and later.

Reprint requests: Dr. John P. Gusdon, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103.

Table I. T and B cell determinations at birth and at six weeks in four erythroblastotic infants whose mothers were treated with promethazine hydrochloride

At birth		*Six weeks*	
T	*B*	*T*	*B*
7 ± 1[1]	6 ± 1.5	41 ± 5.1	14 ± 4.8

Mean ± 1 standard deviation.

We have studied T and B lymphocytes in pregnancies complicated by erythroblastosis. All studies were conducted on patients at the North Carolina Baptist Hospital, Winston-Salem, North Carolina. Lymphocyte preparations and T and B cell determinations were performed according to methods outlined at a World Health Organization workshop.[3] A modification of those methods was used only where indicated.

The results of T and B cell determinations done on the cord blood of erythroblastototic infants are presented in Table I. Using the standard methods of lymphocyte separation, we found an apparently significant suppression of T and B cells at birth in these infants. However, in the process of gradient separation of the lymphocytes from the cord blood samples, we noticed that the cell layer which collected at the Ficoll-hypaque interface was red. This was in distinct contrast to the color of lymphocyte preparations made from

blood collected from their respective mothers at the time of delivery. Those preparations were always white. We studied these cells carefully and found a significant contamination of the lymphocytes by nucleated red cells. When blood from these children was again studied six to eight weeks later with the same methods, we found that the T and B cells had apparently returned to normal. Smears had been made for differential analysis from the cord blood of those erythroblastotic children. We found a range of 89 to 120 nucleated red cells per 100 white cells in those infants. By six weeks of age, the reticulocyte count in these infants had returned to normal levels of 4 per cent or less, coincident with the elevation to apparently normal levels of the T and B cells.

It was not until the fifth erythroblastotic infant that we finally found an effective technique by which we could remove the nucleated red cells from the lymphocyte preparations without negatively affecting the lymphocytes. We found that the simple modification of adding 2 ml. of distilled water to the lymphocyte pellet, dispersing the cells for twenty seconds by pipetting, and then immediately adding a salt solution of sufficient strength to bring the molarity of the solution to 0.15M resulted in lysis of the nucleated red cells only, with retained functional lymphocytes. Cord blood was obtained at the time of delivery of this erythroblastotic infant, and the lymphocytes from the Ficoll-hypaque gradient interface were separated into two halves. Half of these cells were processed in the usual fashion, and half were water lysed. T and B cell determinations were then accomplished in the standard fashion on both samples. The sample that was studied without removal of nucleated red blood cells was read as being 6 per cent T cells and 4 per cent B cells while the other aliquot gave 41 per cent T cells and 15 per cent B cells.

All treated mothers who were studied (five) were found to have normal adult levels of both T and B cells (54 ± 6 T's and 15 ± 3 B's). There was no apparent effect of the promethazine hydrochloride on maternal lymphocyte numbers.

Our first impression that the low levels of T and B cells found in the erythroblastotic newborn infant might be due to the promethazine hydrochloride treatment was erroneous. When contaminating nucleated red cells were removed from the lymphocyte preparation, the levels of T and B cells in the patients studied so far appeared to be normal.

In a recent paper by Rubinstein and associates,[4] the authors have taken a situation with two variables, the disease process erythroblastosis and the treatment promethazine hydrochloride, and, we believe, erroneously attributed the low levels of T and B lymphocytes to the treatment modality.[4] It appears that the disease process and the infants' response to it rather than the treatment are really at fault. However, we are continuing to study the patients we have treated.

REFERENCES

1. Bierme-Alie-Enjalbert, S.: Les formes graves "in utero" de la maladie hemolitique perinatale par incompatabilite rhesus, Thesis, Toulouse, 1967, Centre Regional de Transfusion Sanguine et d'Hematologie.
2. Gusdon, J. P., Jr., Caudle, M. R., Herbst, G. A., and Iannuzzi, N. P.: Phagocytosis and erythroblastosis. I. Modification of the neonatal response by promethazine hydrochloride, Am. J. Obstet. Gynecol. **125:** 224, 1976.
3. Aiuti, F., et al.: IUIS report of a WHO sponsored workshop on identification, enumeration and isolation of B and T lymphocytes from human peripheral blood, Clin. Immunol. Immunopathol. **3:** 584, 1975.
4. Rubinstein, A., Eidelman, A. I., Melamed, J., Gartner, L. M., Kandall, S., and Schulman, H.: Possible effect of maternal promethazine therapy on neonatal immunologic functions, J. Pediatr. **89:** 136, 1976.

Hormonal evaluation of premature menarche produced by a follicular cyst

RALPH G. WIELAND, M.D.
RAFAEL BENDEZU, M.D.
MARVIN C. HALLBERG, M.S.
PETER TANG, M.D.
KENNETH WEBSTER, M.D.

Departments of Medicine, Pathology, and Obstetrics and Gynecology, Case Western Reserve University and Saint Luke's Hospital, Cleveland, Ohio

Ovarian follicular cysts have been reported as a cause of precocious pseudopuberty.[1] The autonomicity of the tumor has been a matter of debate, mainly because of persistence or recurrence of the precocity after puncture of the cyst and in very rare instances after removal. Sensitive assay techniques for gonadotropins and steroid hormones now make it possible to delineate the hormonal profile of these individuals. We have had the opportunity to study a case of precocious pseudopuberty associated with a follicular cyst. Serial determinations of serum gonadotropins, estradiol, and testosterone in the peripheral venous blood and of estradiol in the ovarian vein and cystic fluid for the first time confirm the impression of autonomous estrogen production.

The patient, a 4-2/12-year-old girl, was admitted because of moderate vaginal bleeding of 1 week's duration. Two days before admission the mother had noticed slight enlargement of the nipples. The patient was the product of an 8 month twin pregnancy. She and her twin brother had previously normal development. On examination slight nipple enlargement was noted. No *café au lait* spots were observed. The labia majora were prominent. The clitoris was normal. The rugae

Supported in part by a General Research Support Grant from the National Institutes of Health.

Reprint requests: Dr. Ralph G. Wieland, Saint Luke's Hospital, Cleveland, Ohio 44104.

November 15, 1976
Am. J. Obstet. Gynecol.

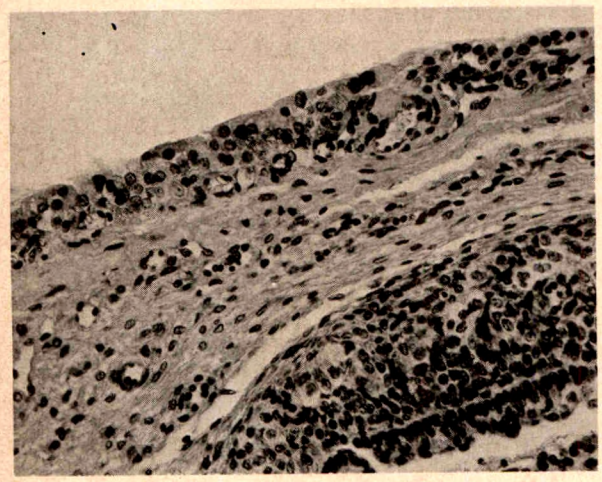


Fig. 1. Microscopic details of the lining of the large cyst (upper margin). Notice the partly luteinized plump theca interna cells. In the right lower corner is a small follicular cyst with partly luteinized plump granulosa and theca interna cells.

of the vagina were hypertrophic. The uterus was small. Examination under anesthesia revealed a 7 to 8 cm. diameter cystic mass in the right adnexa. Vaginal cytology revealed evidence of marked estrogen effect. The bone age was advanced by 1.5 to 2 years over the chronologic age. No radiologic fibrous dysplasia was observed. The urinary 17-ketosteroid excretion was normal (1.5 mg. per 24 hours). The serum cortisol was 9.7 μg per 100 ml. At exploratory laparotomy a fully mobile cystic mass measuring 6 cm. and arising from the right ovary was found. The left ovary was macroscopically normal. A right salpingo-oophorectomy was performed. The pathology report was as follows: The ovary was replaced by a large thin-walled cyst measuring 6 cm. in diameter and weighing 65 Gm. Several smaller cysts were found in the wall. All cysts contained a thin dark red or yellow serous fluid measuring 45 ml. in all. Microscopically (Fig. 1) all cysts were lined by uniform granulosa and theca cells which were often partly luteinized. There were no corpora lutea or albicantia. Some atretic follicles, primordial follicles, and ova were found.

The vaginal bleeding stopped after surgery. Regression of other evidence of precocious development rapidly occurred and has persisted for 12 months. Somatic growth has remained normal for the past year. At 1 year follow-up the bone age had progressed 12 months. X-ray studies of the long bones and calvarium were again normal.

Determinations of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH),[2] estradiol (E_2), and testosterone[3] were performed by radioimmunoassay on peripheral venous serum and of E_2 on right ovarian venous serum and ovarian cystic fluid samples in the pre-, intra-, and postoperative periods. Estradiol was measured by radioimmunoassay following chromatographic separation of serum estrogens on a Sephadex LH-20 column with the S-14 system. One year following surgery venous blood was obtained while the patient was awake and asleep.

The results of the hormonal determinations are shown in Table I. The initial peripheral estradiol level corresponded to

Table I. Hormonal determinations in a patient with a follicular ovarian cyst

Date	*LH (mI.U./ml.)*	*FSH (mI.U./ml.)*	*Estradiol (pg./ml.)*	*Testosterone (n.g/dl.)*
Preoperative	3.0	7.3	33.6	42
Operative				
Cystic fluid			820	
Right ovarian vein			572	
2 hr. postoperative	2.3	6.4	≤2.0*	
48 hr. postoperative	3.8	6.3	≤2.0	48
3 mo. postoperative	1.9	6.2	≤2.0	<40
9 mo. postoperative	7.0	3.1	≤2.0	
12 mo. postoperative				
Awake	1.4	2.7	≤2.0	
Asleep	1.8		≤2.0	

*Lower limit of sensitivity of the assay.

that of an adult female during the follicular phase of the cycle. The right ovarian venous sample indicates that the cyst was the source of estradiol production. The concentration of estradiol in the follicular cyst was somewhat higher than the ovarian venous sample. The testosterone level in the peripheral blood was that of a normal premenopausal adult female.[3] The FSH value was mildly elevated for the patient's age and corresponded to follicular phase concentrations. The LH level was normal for the patient's age. Postoperatively there was a trend toward a decrease in the gonadotropin levels. The values at surgery do not appear to represent levels suppressed by endogenous estrogen. The LH values 1 year later did not show an increase during sleep.

Precocious pseudopuberty is the condition in which the pituitary-gonadal axis is not functioning in a normal fashion as distinguished from "true" precocious puberty. Secondary sexual characteristics develop as a consequence of autonomous sex hormone production. With the advent of sensitive techniques for the radioimmunoassay of gonadotropins and sex steroids the possibilities of a more accurate differential diagnosis and follow-up are enhanced. The autonomous nature of the follicular cyst is supported by the following observations: (1) the rapid and sustained fall of circulating E_2 following cyst removal, (2) the rapid and continued regression of the sexual precocity, (3) normal gonadotropin levels during remission, (4) the normal opposite ovary and (5) the absence of an LH increase during sleep.

We express our gratitude to Dr. Burton V. Caldwell, Department of Obstetrics and Gynecology, Yale University, for his generous gift of estrogen antiserum. The materials for iodination for the FSH and LH assays and the FSH antiserum (Batch No. 3) were provided by the Natioanl Institutes of Health.

REFERENCES

1. Monteleone, J. A., Monteleone, P. L., and Danis, R. K.: Pseudoprecocious puberty associated with isolated follicular cyst of the ovary, J. Pediatr. Surg. **8:** 949, 1973.
2. Guevara, A., Vidt, D., Hallberg, M. C., Zorn, E., Pohlman, C., and Wieland, R. G.: Serum gonadotropin and testosterone levels in uremic males undergoing intermittent dialysis, Metabolism **18:** 1062, 1969.
3. Wieland, R. G., Zorn, E. M., Hallberg, M. C., and Furst, B.: Testosterone and metabolites in women using radioimmunoassay techniques, *in* Curry, A. S., and Hewitt, J. V., editors: Biochemistry of Women; Methods for Clinical Investigation, Cleveland, 1974, CRC Press, p. 181.

Torsion of the oviduct following laparoscopic sterilization

HOWARD I. SHAPIRO, M.D., F.A.C.O.G.
WILLIAM F. HUGHES, M.D., F.A.C.S.
DANIEL H. ADLER, M.D., F.A.C.O.G.

Department of Obstetrics and Gynecology, The Norwalk Hospital, Norwalk, Connecticut

TORSION of the oviduct is an extremely rare gynecologic condition which is seldom if ever diagnosed preoperatively. There are fewer than 400 cases in the world's literature, and only three cases following Pomeroy tubal ligation. To our knowledge, this is the first report of tubal torsion following laparoscopic sterilization.

Reprint requests: Howard I. Shapiro, M.D., 131 Kings Highway North, Westport, Connecticut 06880.

D. P., a 35-year-old woman, para 2-0-0-2, underwent an uneventful laparoscopic tubal coagulation and excision on May 9, 1974. Via a single umbilical incision, the tubes were coagulated and cut 2 cm. from their insertion into the uterus. The patient was discharged on the day of surgery.

On January 13, 1975, she was examined by her physician following the sudden onset of intermittent right lower quadrant pain. Though she appeared to be in great distress, the temperature was 99° F., rebound tenderness in the right lower quadrant was minimal, and bowel sounds were normal. On pelvic examination, there was slight cervical tenderness to motion and a fullness in the right adnexa, although no definite mass was palable. The white blood cell count was 9,300, with a normal differential. A presumptive diagnosis of pelvic inflammatory disease was made, and ampicillin prescribed.

On January 15, 1975, she was admitted to Norwalk Hospital. Rebound tenderness was now present over the entire upper and lower abdomen. Bowel sounds were hypoactive and hyperresonant, and the temperature was 101° F. The white blood cell count was now 11,900 with 82 polymorphonueclear leukocytes, four stab cells, and 14 lymphocytes. The sedimentation rate was 37. Exploratory laparotomy was performed. A small amount of serosanguineous fluid was noted in the peritoneal cavity. The distal portion of the right oviduct was in complete torsion, and distended to a length of 10 cm. and a diameter of 5 cm. (Fig. 1.) A right salpingectomy and appendectomy were performed. The postoperative course was uneventful. The microscopic appearance of the oviduct was one of the hemorrhagic necrosis with dilated blood vessels containing thrombi.

The etiology of tubal torsion remains obscure. Provost[2] cited both intrinsic and extrinsic factors which may predispose to this condition. The former include excessive length of the tube, hydrosalpinx, tubal ligation, tubal neoplasm, incomplete distal mesosalpinx,

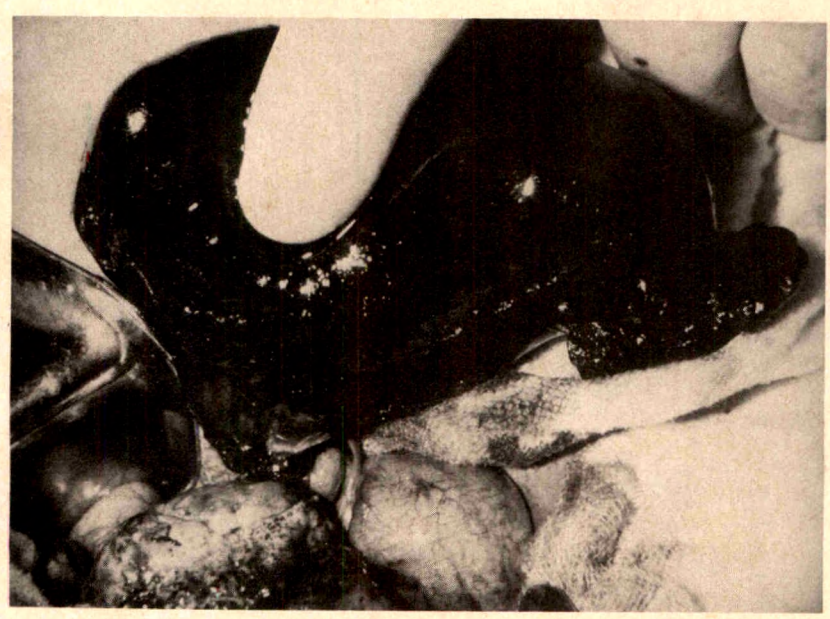


Fig. 1. Twisted oviduct, fimbria on right, noted at laparotomy.

and abnormal tubal peristalsis. Extrinsic factors which he listed are ovarian tumors, uterine enlargement by pregnancy or tumor, adhesions to the tube, sudden movement or trauma, pelvic congestion, and drug reaction with tubal spasm. One can only speculate that our patient's problem resulted from cutting too deeply into the mesosalpinx, thereby allowing too much rotation and movement of the distal portion of the oviduct. The symptoms with which our patient presented are typical of tubal torsion. The pain is characteristically right-sided, of sudden onset, intermittent, and of far greater intensity than the clinical and laboratory findings would indicate. Initially, abdominal rigidity is usually absent or not pronounced. This is often helpful in distinguishing this condition from appendicitis. Other differential diagnoses include ureteral colic, twisted ovarian cyst, ectopic pregnancy, acute salpingitis, and ruptured follicle cyst.

REFERENCES

1. Kendrick, J. G.: Torsion of the tube following Pomeroy sterilization, Obstet. Gynecol. **25:** 124, 1965.
2. Provost, R. W.: Torsion of the normal Fallopian tube, Obstet. Gynecol. **39:** 80, 1972.

Changes in congenital oral cleft incidence in relation to induced abortions

ANTHONY P. POLEDNAK, PH.D.

Birth Defects Institute, State Department of Health, Albany, New York

FRANK A. OSKI, M.D.

Department of Pediatrics, College of Medicine, State University of New York, Syracuse, New York

RESULTS OF animal studies suggest that maternal stress is associated with congenital oral clefts. Fraser and Warburton's[1] findings on "emotional stress" in pregnant women do not support the hypothesis of a relation with cleft lip or palate. In a retrospective study, however, Saxen[2] reported a significant difference between case and control mothers in reporting of "emotional stress" in the first and second trimesters. The higher number of smokers and alcohol consumers among mothers of children with clefts could also indicate a role of "emotional factors."[2] Prospective studies are needed.

Data from the Abortion Surveillance Program of the Center for Disease Control indicate that in a high proportion of women having legal abortions the stated reason for abortion was "mental health," in those states in which a reason is required by law. Further studies are needed to determine to what extent psychological stress or psychiatric illness is an incentive for having an abortion.

Reprint requests: Dr. Anthony P. Polednak, Center for Human Radiobiology, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, Illinois 60439.

Table I. Incidence rates of congenital oral clefts and total malformations among live births, upstate New York, 1963-1973

Year	*No. of oral cleft births*	*Total live births*	*Rate per 10,000 live births*	*Total malformations, rate per 10,000 live births*
1973	121	126,259	9.58	95.99
1972	133	134,218	9.91	95.29
1971	162	149,646	10.83	105.11
1970	197	165,208	11.92	109.86
1969	201	161,099	12.48	125.39
1968	195	157,688	12.37	120.05
1967	205	159,179	12.88	112.77
1966	203	164,273	12.36	104.10
1965	190	173,262	11.00	112.08
1964	247	182,352	13.55	124.27
1963	231	184,506	12.52	112.30

If various types of maternal "stress" were causally related to congenital oral clefts in offspring, and if pregnant women under stress had high induced abortion rates, an effect on congenital oral cleft incidence rates could be expected after induced abortion became more readily available. That is, with selective removal (by induced abortion) of fetuses at high risk for oral clefts due to maternal stress, a decline in incidence of congenital oral clefts would be expected.

The present data refer to live births recorded in upstate New York, to residents of that region, from 1963 to 1973. Information on congenital malformations was obtained from birth certificates. Other vital statistics, including induced abortions and live births, were obtained from the Office of Biostatistics of the State Health Department. All birth certificates reporting oral clefts were enumerated; this category includes congenital cleft lip, cleft palate, and cleft uvula. Comparison of rates before and after the legalization of induced termination of pregnancy in 1970 in New York State provides a partial test of the hypothesis that self-selection for induced abortion by pregnant women under stress could lead to a decline in congenital oral cleft rates.

Table I shows that incidence rates for congenital oral clefts were fairly stable until 1970, at which time a decline appears to have begun. Comparing 1969 with 1973, a considerable decrease is observed (12.48 vs. 9.58 per 10,000, or a 23.2 per cent reduction). The total malformation rate also declined from 1969 to 1973. Again comparing 1969 to 1973, the decline in incidence rate for total malformations (125.39 vs. 95.99 per 10,000, or a 23.4 per cent reduction) is comparable to that observed for oral clefts alone (i.e., 23.2 per cent). This suggests that some broad demographic or

Table II. Changes in congenital oral-cleft incidence rates by maternal age

Maternal age	*1963-70 rate per 10,000*	*1971-73 rate per 10,000*	*Change in rate*	*Per cent change**	*Induced abortions per 1,000 live births, 1971-73*
< 20	12.36	9.89	−2.47	−20.0	501
20-24	11.94	9.37	−2.57	−21.5	189
25-29	12.46	9.67	−2.79	−22.4	110
30-34	12.12	12.32	+0.20	+1.7	125
35-39	13.54	12.50	−1.04	−7.7	338
40+	15.81	12.79	−3.02	−19.1	611
Total	12.38	10.15	−2.23	−18.0	217
Total no. of oral-cleft births	1,668	416			
Total no. of live births	1,346,990	409,955			

*Change in rate divided by rate in 1963-70.

environmental changes may have occurred that affected several types of malformations.

A more specific test of the hypothesis of an effect of induced abortions on incidence rate of oral clefts involves analysis by maternal age. If legalized abortion had an effect, the reduction in the rate should be greatest at the extremes of maternal age, since induced abortions are more frequent at these ages. Table II shows the ratio of induced abortions to live births in upstate New York among upstate residents. Comparing 1963-1970 with 1971-1973, the magnitude of the decline in the oral cleft rate is approximately equal in the first three maternal age categories (<20, 20-24, and 25-29), whereas the induced abortion/live birth ratio declines sharply after age 19. The decline in the oral cleft rate is greater at maternal age 40 and over than at 30-39 years, but the over-all correspondence between the per cent change in oral cleft rate and the abortion rate is not very close. Thus, analysis of oral cleft incidence rate by maternal age before and after the 1970 abortion law does not provide strong support for a simple causal relationship.

The pattern of decline in oral clefts by maternal age (Table II) could still conceivably be explained by selective removal by induced abortion of fetuses at high risk for oral clefts due to the effects of maternal stress, since reasons for seeking abortion may vary with maternal age. For example, psychological stress may be more frequent, or a more common incentive for abortion, at certain maternal ages.

Finally, it should be noted that some fetuses with oral clefts (or other malformations) which would have aborted spontaneously are induced to abortion. The occurrence of oral clefts in spontaneous abortions is noteworthy in this connection, as is the higher frequency of threatened abortion in pregnancies leading to oral clefts compared with controls. Chromosomal abnormalities are associated with some cases of oral clefts and with risk of spontaneous abortion. Thus, even without induced abortions some fetuses with oral cleft would never survive to birth. Hence, any reduction in oral cleft incidence at birth related to induced abortions may be difficult to detect.

REFERENCES

1. Fraser, F. C., and Warburton, D.: Plast. Reconstr. Surg. **33:** 395, 1964.
2. Saxen, I.: Int. J. Epidemiol. **3:** 263, 1974.

Thoracopygopagus tripus: An unusual form of conjoined twins

EDWARD M. LICHTEN, M.D.
NICHOLAS J. TETERIS, M.D.
Ohio State University Hospital, Columbus, Ohio

THE PATHOLOGIC anatomy of a rare form of conjoined twins is presented. The criteria for antenatal and obstetric management are reviewed.

A 31-year-old Gl, PO, ABO Caucasian nurse, gravida 1, para 0, with a blood type of AB-negative, was followed at the Ohio State University Hospital's obstetric clinic from her fourteenth week of gestation. She presented on February 12, 1974, with a 12 hour history of spontaneously ruptured membranes. No history of exposure to any known teratogens was elicited. No prenatal drug or viral exposure was extracted. Family history was negative for twinning; twins were not suspected prior to admission.

The patient's last menstrual period was on July 14, 1973; the estimated date of confinement was April 22, 1974. On admission the patient reported extensive fetal movement in the lower quadrants. Physical examination was normal. The uterus measured 38 cm. at a calculated gestational age of 34 weeks. Two heads were felt in the epigastrium with no presenting part in the pelvis. The cervix was undilated. A flat plate of the abdomen confirmed the presence of twins. The antenatal diagnosis of conjoined twins was entertained because of the symmetrical relationship of the twins. Vaginal delivery was attempted by Pitocin augmentation. Intravenous pitocin concentration was increased over 7 hours from 1 to 6 m.u. per minute. Although pelvimetry was quite adequate,

Reprint address: Edward M. Lichten, M.D., East Baptist Hospital, Doctor's Building, 3950 Kresge Way, Louisville, Kentucky 40207.



Fig. 1. Gross pathology of conjoined twins with fused third leg.

descent did not occur. Cesarean section was performed through a low transverse cervical incision. The fetuses were delivered with ease with no evidence of respiratory or cardiac activity.

The combined fetal weight was 2,850 grams. The bodies were first fused at the sternum with four clavicles. An anterior and a posterior sternum were noted with a single pericardial space and fused common liver. Twin "A" had a right-sided aortic arch, with an anomalous origin of the left subclavian off the descending portion of the arch, and a left-sided superior vena cava, with a prominent right-sided brachiocephalic vein crossing the midline. Twin "B" had a normal left-sided aortic arch, with an anomalous origin of the right subclavian artery passing dorsally to the esophagus and trachea. Twin "B" demonstrated a patent ductus arteriosus; Twin "A" showed 90 per cent occlusion. A single umbilical vein noted entering the region of the porta hepatis communicated with the inferior vena cava of Twin "A" and could be dissected through the sinus intermedius to the regious on the portal vein of Twin "B."

The respiratory system contained normal structures, with "A" having three lobes on the left and two on its

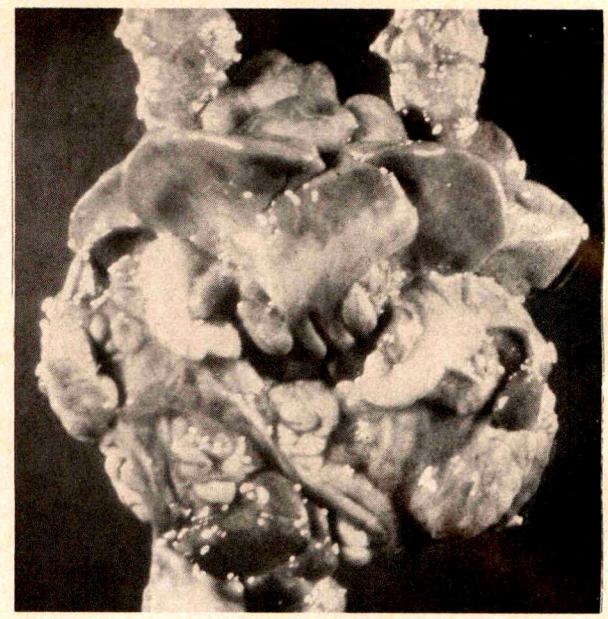


Fig. 2. Internal anatomy showing fused liver and two stomachs with sinus inversus of twin "A".

right; "B", two on the left and three on the right. However, the gastrointestinal tract of Twin "A" showed situs inversus in reference to a normal-positioned "B". Two separate jejunae were noted. The rectal regions in both gastrointestinal systems ended in a blind pouch.

The urinary system was unusual in that both twins had two kidneys, two ureters, and a bladder, but the left kidney of Twin "B" communicated with an anterior bladder as did the right kidney of Twin "A." The posterior bladder emptied the remaining two kidneys. The urethras connected with the perineum through a common opening.

The genital system demonstrated an anterior vagina which ended as a blind pouch. It joined with the anterior bladder through a urethal-vaginal fistula. The cervix, bicornuate uterus, two oviducts, and two ovaries were separated from the posterior genital system by the rectal pouches. The posterior genital system had a double imperforate vagina. The left one communicated with the posterior bladder through a urethral-vaginal fistula. The uterus was bicornuate with two oviducts and ovaries. A double cervix was noted. The right ureter of Twin "B" crossed the rear surface of the back uterus to join the posterior bladder.

The twins shared an ilium from which the common third leg originated.

The antenatal diagnosis of conjoined twins was made radiographically based on Gray's criteria. Vaginal delivery was noted in 60 per cent of reported cases and should be considered if gross structural abnormalities were to be discovered. If a difficult delivery was expected due to birth weight over 8 pounds, or if surgical

correction was considered, cesarean section was probably the best mode of delivery.

The majority of pygopagus and ischiopagus twins with common pelves would have the cross-communicating urinary system described in this case report. If surgical intervention could be postponed, surgical prognosis was greatly improved. Failure of one infant was indication for immediate intervention.

REFERENCES

1. Guttmacher, A. F., and Nichols, B. L.: Birth Defects **3:** 3, 1967.
2. Zimmerman, A. A.: Birth Defects **3:** 18, 1967.

The prepartum diagnosis of conjoined twins by the use of diagnostic ultrasound

ROBERT L. WILSON, M.D.
CURTIS L. CETRULO, M.D.
MICHAEL S. SHAUB, M.D.

Departments of Radiology and Obstetrics and Gynecology, Los Angeles County/University of Southern California Medical Center, Los Angeles, California

THE EARLIEST known and recorded case of conjoined (Siamese) twins was in Kent, England, in 1100 A.D. They were known as the Biddenden Twins and lived to the third decade of life. Since that time, approximately 500 cases of conjoined twins have been described[1, 2] and their incidence has been estimated at one in every 50,000 deliveries to one in every 100,000 deliveries.[1, 2] The rare occurrence of such an anomaly makes the statistics difficult to rely upon.

Prior to 1950, only four cases had been diagnosed or strongly suspected prior to labor.[1, 2] The ultrasound findings in conjoined twins have never before been described in the antepartum period and are included herein.

Margarita M. was a 34-year-old Mexican-American woman, gravida 5, para 4, with four normal children. The previous pregnancies were uncomplicated and produced term-sized infants: 3 boys and 1 girl. Her last normal menstrual period was on January 4, 1974, with an expected date of confinement of October 11, 1974. There was no consanguinity but there was a strong family history of twins. Following the last delivery, in 1971, a right unilateral tubal ligation was performed. The left adnexa was described as being "surgically absent."

The patient was followed at an outside clinic and was first seen at 10 weeks' gestation. The uterus at that time was felt to be compatible with a 14 week gestation. Two other subsequent examinations yielded a fundal height larger than the gestational age. At 35 weeks' gestation, the fundal height measured 41 cm. and a radiograph was obtained to exclude the possibility of twins. Two fetuses were identified, both in the breech position, *en face*. The patient was then referred to the L. A. County/USC Medical Center for further care and diagnosis, including an ultrasound examination. The ultrasound procedure performed on September 20, 1974, demonstrated two fetuses in the breech position with an estimated mean gestational age of approximately 37 weeks. Two separate, distinct thoraces could not be demonstrated and only one fetal heart rate, in the midline, could be heard on Doppler examination. The diagnosis of conjoined (Siamese) twins was verbally entertained, but the radiograph was not available for confirmation.

In addition to the usual prenatal medications, the patient was placed on Ritodrine HCl, a beta-sympathomimetic agent, at 35 weeks' gestation. The Ritodrine was administered prophylactically in order to reduce the risk of premature labor. The patient entered the emergency room on October 12, 1974, complaining of spontaneous uterine contractions with spontaneous rupture of membranes shortly thereafter. Subsequent labor produced a double footling breech and a primary cesarean section was elected. The patient was taken to the operating room and prepared in the usual manner. Induction of general anesthesia to delivery time required 12 minutes. Female thoracopagus twins were delivered through a low transverse incision without extension or complication. The left adnexa was present and a left unilateral tubal ligation was performed. The Apgar scores were 1 at 1 minute and 4 at 5 minutes. The combined weight was 4,590 grams. Soon after delivery, the babies were placed on separate respirators which alternately ventilated them. Numerous complications developed and their clinical status rapidly deteriorated. The babies died approximately 12 minutes apart on October 15, 1974. The complete autopsy findings are beyond the scope and purpose of this report, but of interest was the finding of a single pericardium and a common right ventricle. The twins were joined from the level of the xyphoid sterni to the lower midabdomen in the region of the hypogastrium.

The case presented allows confirmatory radiographic and ultrasonographic findings to be summarized for the first time in an instance of thoracopagus conjoined twins. Although conjoined twins are a rare entity, thoracopagus is, by far, the most common form of this anomaly.[1, 2] An incidental autopsy finding in many of the reported thoracopagus twins was the occurence of a single, common pericardium.[1, 2] When confronted with the ultrasound findings of a single trunk outline, one persistent heart rate by Doppler examination, and the radiographic criteria described by Gray,[1, 2] the physician should be highly suspicious of the presence of thoracopagus twins. Other types of conjoined twins will alter these findings accordingly.

Reprint requests: Robert L. Wilson, M.D., Chief, Diagnostic Ultrasound Section, Department of Radiology, Department of Health Services, Los Angeles County-University of Southern California, 1100 N. Mission Rd., Los Angeles, Calif. 90033.

REFERENCES

1. Tan, K. L., Goon, S. M., Salmon, Y., and Wee, J. H.: Acta Obstet. Gynecol. Scand. **50:** 373, 1971.
2. Birth Defects Original Article Series, National Foundation-March of Dimes **3:** No. 1, April 1967.

November 15, 1976
Am. J. Obstet. Gynecol.

Fetal monitoring during cesarean section

MARIAN DE MARINIS
LESLIE S. LEIGHTON
JOHN W. C. JOHNSON, M.D.

Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland

ALTHOUGH a great deal of research and development has been expended in improving fetal monitoring during labor and vaginal delivery, very little consideration has been given to fetal monitoring during the course of cesarean section delivery. Certainly the obstetric complications necessitating abdominal delivery, or the hazards associated with the required major anesthesia, pose high-risk situations for the fetus.[1, 2] The time interval from initiation of anesthesia until section delivery occasionally extends to 30 or 45 minutes, yet fetal assessment during this dangerous period is rarely satisfactory. Utilization of the lower abdomen for the surgical procedure precludes the use of standard monitoring techniques other than the fetal scalp electrode. In this hospital, the latter technique is available in only 25 to 30 per cent of cases which come to cesarean section delivery. The risk of maternal infection associated with delivering the attached scalp electrode from the vagina through the uterine and abdominal incisions makes even this technique less than optimal for monitoring abdominal delivery. The purpose of this study was to determine whether placement of ultrasound transducers in positions other than the lower abdomen might be applicable to fetal monitoring during the preparatory steps and performance of cesarean section delivery.

In an attempt to identify alternate positions for monitoring, Doppler ultrasound transducers* were applied to the upper abdomen, the flank, the back, and within the vagina in patients beyond 34 weeks of gestation. Transducers placed within the vagina were first disinfected by a 10 minute immersion in buffered glutaraldehyde solution.† They were immediately rinsed in sterile water and dried with a sterile towel prior to being placed in the posterior fornix, adjacent to the presenting part. A viscous conducting jelly was applied liberally to the face of the transducer in all cases.

The results of this study indicate that the fetal heart rate is best detected by placing the transducer in the midline of the abdomen just superior to the umbilicus. Acceptable fetal pulse signals were obtained in 46 out of 51 patients (90 per cent) monitored in this fashion. Placement of the transducer within the vagina permitted detection of the fetal pulse in 25 out of 30 cases (83.3 per cent). Attempts to detect the fetal pulse by placing monitors on the maternal back or flank were generally unsuccessful.

To date, 25 cesarean sections have been monitored successfully by placement of the transducer either on the upper abdomen or within the vagina. In obese patients and in fetal malpresentations, monitoring from the upper abdomen may be difficult, but generally can be achieved by fastening the transducer with adhesive tape into the position of maximal fetal pulse detection. In those occasional cases where the fetal pulse becomes undetectable, an assistant can adjust the position of the transducer while the lower abdomen is being prepared and draped for surgery. After draping, the operative assistant can manipulate the transducer probe from above and through the drapes. The experience to date has been that in those few cases where upper abdominal positioning is initially unsatisfactory, vaginal placement is a suitable alternative. Although disinfection of the probe was used in this pilot study, sterilization would be the optimal preparation for routine vaginal placement. This could be accomplished either with gas (ethylene oxide 12 per cent and dichlorodifluoromethane 88 per cent) sterilization or 10 hour immersion in buffered glutaraldehyde.

The monitors utilized in this study do not provide an instantaneous and written record of the fetal heart rate. However, the audible signal is such that the operating team is alerted to moderate or severe decelerations in the fetal pulse rate. Under such circumstances, fetal supportive measures can be instituted quickly. Precautions always must be taken to differentiate maternal from fetal pulse signals. In those operating units where maternal electrocardiographic monitoring is routinely employed, this is readily accomplished. Otherwise, an assistant can distinguish the maternal pulse rate by either palpation or auscultation.

In summary, we have found that fetal heart rate monitoring can be conveniently accomplished during cesarean section by positioning a Doppler transducer either on the maternal upper abdomen or within the vagina. Fetal monitoring during the induction of anesthesia, the preparation of the surgical field, and the actual operative procedure would appear to be an important adjunct to reducing the fetal and neonatal morbidity associated with cesarean section delivery.

Reprint requests: John W. C. Johnson, M.D., Department of Gynecology and Obstetrics, the Johns Hopkins Hospital, Baltimore, Maryland 21205.

*Echotone Ultrasonic Doppler, Syntex Medical Instruments, Division of Metrix, Inc., Denver, Colorado.

†Cidex, Arbrook Inc., P.O. Box 130, Arlington, Texas 76010.

REFERENCES

1. Benson, R. C., Shubeck, F., Clark, W. M., et al.: Fetal compromise during elective cesarean section. A report from the collaborative project. AM. J. OBSTET. GYNECOL. **91:** 645, 1965.
2. Marx, G. F., Cosmi, E. V., and Wollman, S. B.: Biochemical status and clinical condition of mother and infant at cesarean section, Anesth. Analg. **48:** 986, 1969.

INDEX TO ADVERTISERS

Abbott Laboratories
Fero-Folic-500/Iberet-Folic-500 ——— 20, 21
Ogen ——— 42, 43, 44

Ayerst Laboratories
Premarin ——— 37, 38, 39, 40

Baylor College of Medicine
Postgraduate Course ——— 29

Carnrick Laboratories
Hormonin ——— 6

Corometrics Medical Systems, Inc.
Fetal Monitor ——— 25

Frigitronics of Connecticut Inc.
Frigi Colposcope ——— 10

Hamot Medical Center
Classified ——— 29

Holland-Rantos Co., Inc.
Koromex ——— 18

MDT Corporation
Chemiclave and Vibraclean ——— 14

Madison General Hospital
Classified ——— 45

Masson Publishing USA, Inc.
Books ——— 36

Mead Johnson Laboratories
Estrace ——— 26, 27, 2
Peri-Colace ——— Fourth Cove

Merrell-National Laboratories
AVC ———

Ortho Pharmaceutical Corporation
ModiCon ——— 46, 47, 4
Monistat ———
Ortho-Novum 1/80 ——— 31, 3
Sultrin ——— 34, 3

Purdue Frederick Company
Senokot S ———

Searle & Co., G.D.
Cu-7 ——— Second Cover,
Ovulen ——— 15,

Storz Endoscopy, Karl-America, Inc.
Laparoscopes ——— 2

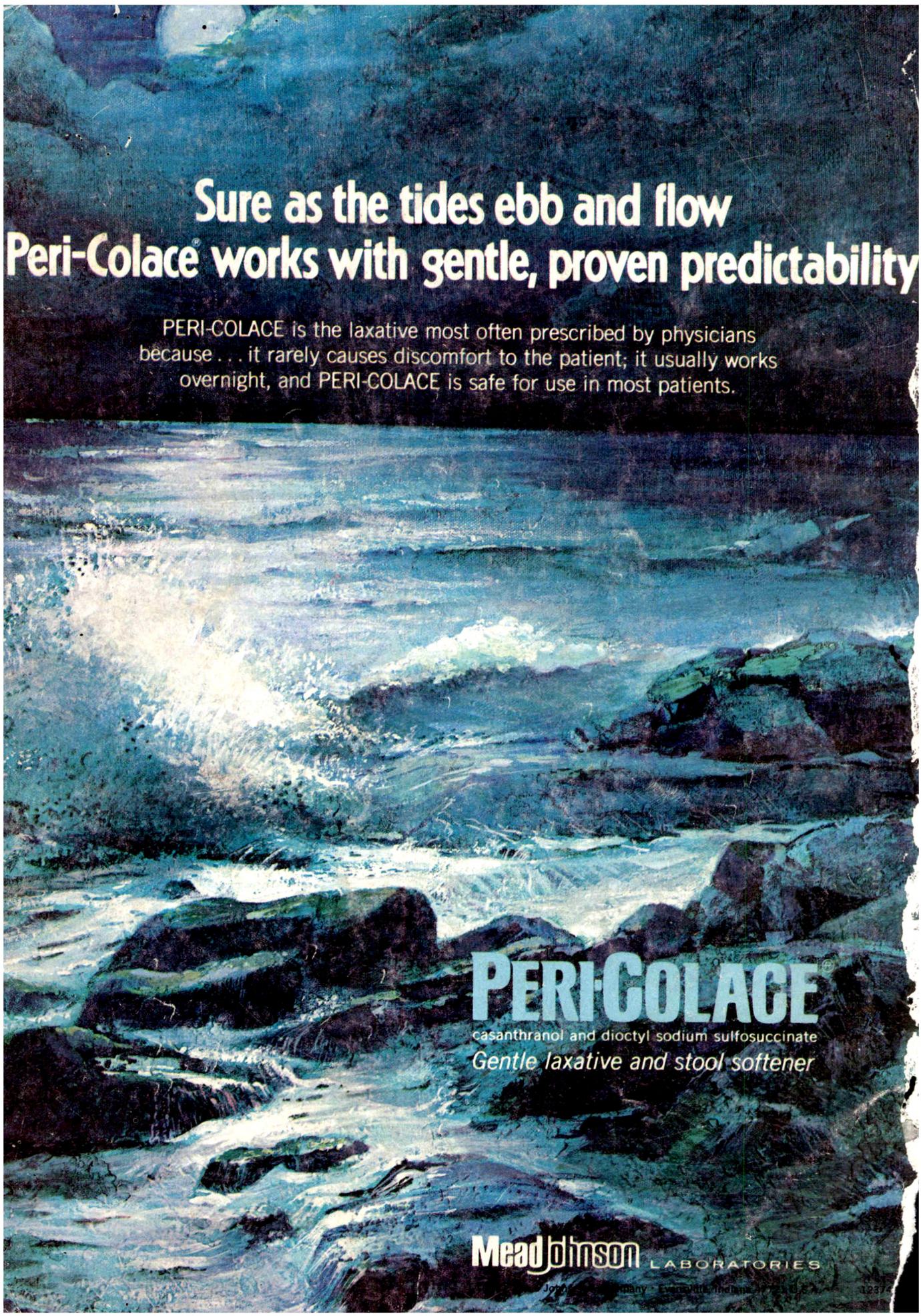
University of Tennessee
Classified ———

University of Utah
Classified ———

Welch Allyn, Inc.
Disposable Vaginal Specula ———

Wyeth Laboratories
Lo/Ovral ——— 22, 23
Ovral ———

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index


Sure as the tides ebb and flow
Peri-Colace® works with gentle, proven predictability
PERI-COLACE is the laxative most often prescribed by physicians because . . . it rarely causes discomfort to the patient; it usually works overnight, and PERI-COLACE is safe for use in most patients.
PERI-COLACE®
casanthranol and dioctyl sodium sulfosuccinate
Gentle laxative and stool softener
Mead Johnson LABORATORIES